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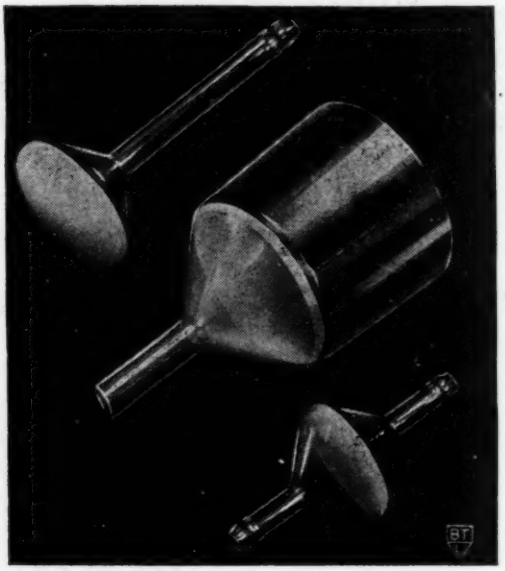

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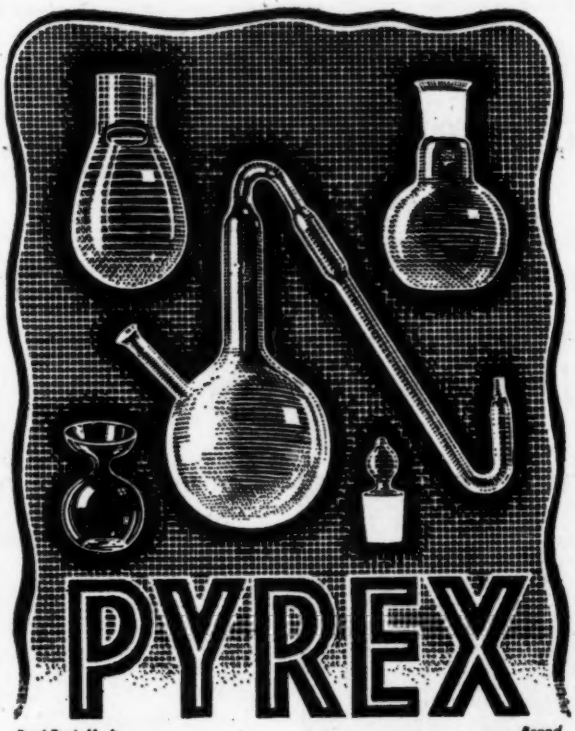

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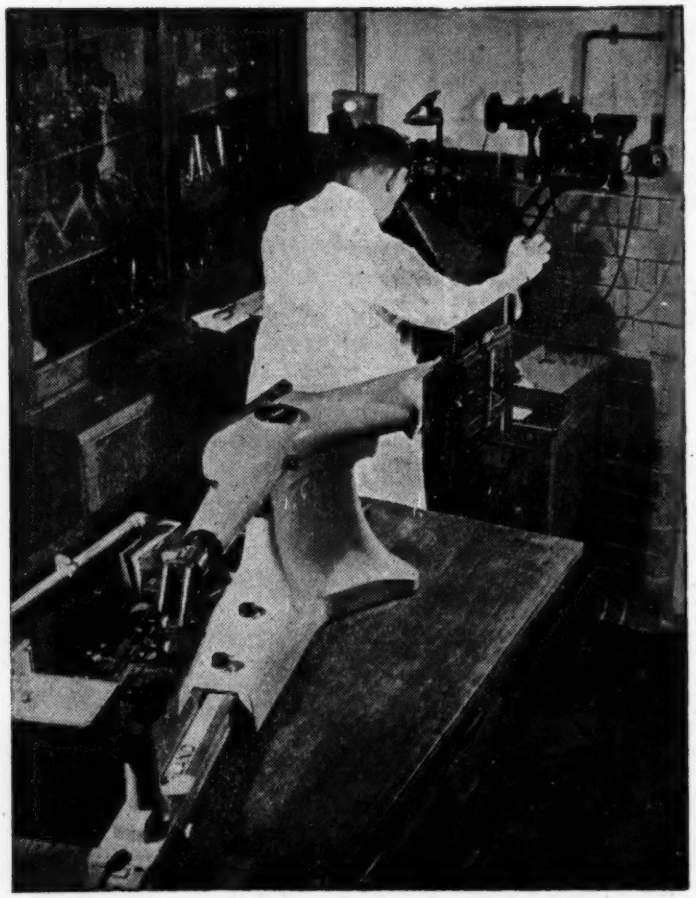

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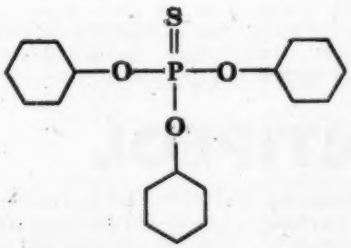

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460	6	*for* "$\overset{\oplus}{C}$–NH_3" *read* "C–$\overset{\oplus}{N}H_3$."
461	22 *	*delete* "the distillate."
461	40	*for* "p. 460" *read* "p. 459."
534	20 *	*for* "$<$99%" *read* "$\leqslant$99%."
659	5	*for* "0·166 g." *read* "1·66 g."

Vol., 1944.

9	34	*for* "6·2 g." *read* "2·0 g."
10	23 *	*for* "in this reaction formaldehyde is produced" *read* "in this reaction no formaldehyde is produced."
90	9 *	*for* "180°" *read* "18°."

* From bottom.

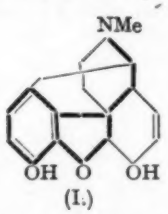
68. *Synthetic Analgesics. Part I. Synthesis of Basic Benzofuran Derivatives and certain 4-Phenylpiperidine Compounds.*

By F. Bergel, J. W. Haworth, A. L. Morrison, and H. Rinderknecht.

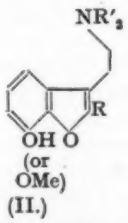
Attempts to synthesise basic benzofuran derivatives as forming part of the morphine molecule and possibly possessing analgesic properties are described. Although 3-β-dialkylaminoethylcoumarones could not be obtained from 2-hydroxy-β-dialkylaminopropiophenones, yet *2-dimethylaminomethyl-6-methoxycoumaranone* and *2-β-piperidinopropionyl-7-methoxycoumarone* were synthesised. By using the method of Eisleb (*Ber.*, 1941, **74**, 1433) *4-(2′-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid lactone* and its *3′-methoxy*-analogue were prepared from the corresponding phenylacetonitriles. A related *coumaran* was obtained when *4-acetyl-4-(2′-methoxyphenyl)-1-methylpiperidine*—from the corresponding nitrile with methylmagnesium iodide—was reduced, and the product treated with concentrated hydrobromic acid. Attempts to reduce 4-arylpiperidine-4-nitriles with sodium and alcohol to primary amines failed, for the nitrile group was removed; on catalytic hydrogenation the secondary amine was formed.

The synthesis of true analgesics has long been the object of research; work in this field before 1938 has been adequately reviewed by Fourneau (*Chim. Ind.*, 1938, **39**, 1043) and by Small, Eddy, Mosettig, and Himmelsbach (Publ. Health Service, Suppl. No. 138, U.S. Treasury Dept., Washington, 1938). Much attention has been directed to the study of synthetic substances whose structures embrace certain features found in the morphine molecule (I), but although some such compounds show promising pharmacological properties, none so far obtained can seriously compete with morphine or a number of its derivatives.

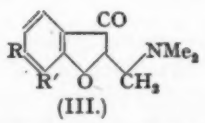
In taking up the study of synthetic analgesics, we decided first to attempt the preparation of basic derivatives of benzofuran which forms part of the morphine molecule, for this group has not been studied previously. Although we then failed to prepare representatives of 3-β-dialkylaminoethylcoumarones or coumarans of type (II; R′ = alkyl), we did prepare a 2-dialkylaminocoumaranone (cf. III) and a 2-β-piperidinopropionylcoumarone derivative (cf. IV).



(I.)



(II.)



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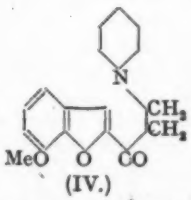
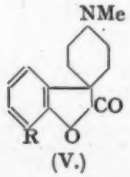


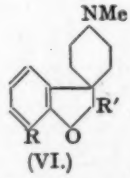
(IV.)

While we were engaged on the above work, Eisleb and Schaumann (*Deut. med. Wochenschr.*, 1939, **65**, 967) announced the synthesis of a new analgesic, ethyl 4-phenyl-1-methylpiperidine-4-carboxylate. Methods for its preparation and that of similar piperidine derivatives were later reported by Eisleb (*Ber.*, 1941, **74**, 1433) and in patent literature (B.P. 501,135; U.S.PP. 2,167,351, 2,242,575), and the pharmacological properties of 42 compounds of this series were described by Schaumann (*Arch. Path. Exp. Pharm.*, 1940, **196**, 109).

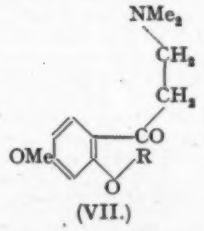
In view of the interesting physiological properties of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (Dolantin, Dolantal, Demerol, or, according to the British Pharmacopœia Commission, Pethidine) and its close relation to substances of our own working scheme, we extended our original work to the preparation of *iso*-coumaranones of type (V) and of a coumaran of type (VI), using Eisleb's general method (*loc. cit.*) for the preparation of the required 4-phenylpiperidine-4-nitriles in which phenylacetonitriles are condensed with ββ′-dichlorodiethylamines. We have also obtained several other new 4-phenylpiperidine compounds.



(V.)



(VI.)



(VII.)

In our first experimental series we prepared from 2-hydroxy-4-methoxyacetophenone (pæonol) with paraformaldehyde and secondary bases (cf. Mannich, *Ber.*, 1922, **55**, 356) *β-dimethylamino-2-hydroxy-4-methoxypropiophenone* (VII; R = H), its *2-acetoxy*-derivative (VII; R = Ac), and *β-piperidino-2-hydroxy-4-methoxypropiophenone*. The glycollic acid or ethyl glycollate ether of pæonol, treated in a similar manner, yielded *2-β-dimethylaminopropionyl-5-methoxyphenoxyacetic acid* (VII; R = $CH_2{\cdot}CO_2H$), its *ethyl* ester, and the two corresponding *piperidino*-compounds. When the potassium salt of (VII; R = H) was treated with an α-halogeno-ketone, according to the method of Kunkell and Kessler (*Ber.*, 1903, **36**, 1260), who prepared 2-benzoyl-3-methylcoumarone from *o*-hydroxyacetophenone and ω-bromoacetophenone, the desired coumarone (cf. II; R = COPh) was not formed; instead, when ω-bromoacetophenone was used, only ω-dimethylamino-

acetophenone and 2-hydroxy-4-methoxyphenyl vinyl ketone could be isolated. When (VII; R = $CH_2 \cdot CO_2H$) or its ethyl ester was caused to react with acetic anhydride and sodium acetate, according to Kostanecki and Tambor's conditions (*Ber.*, 1909, **42**, 905), again the molecule was disrupted.

On the other hand, when (VII; R = Ac) was brominated to *α-bromo-β-dimethylamino-2-acetoxy-4-methoxypropiophenone* and the acetyl groups removed with hydrobromic acid, the free phenol yielded with potassium carbonate in acetone the very unstable 2-dimethylaminomethyl-6-methoxycoumaranone (III; R = OMe, R′ = H).

Another basic benzofuran derivative was prepared when *7-methoxy-2-acetylcoumarone*, obtained from *o*-vanillin with chloroacetone in presence of potassium hydroxide according to Stoermer (*Ber.*, 1903, **36**, 2865), was condensed with paraformaldehyde and piperidine hydrochloride to give *2-β-piperidinopropionyl-7-methoxycoumarone* (IV).

Eisleb's method enabled us to approach our original goal (cf. II) to some extent. First, we prepared the *iso*coumaranones, *4-(2′-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid lactone* (V; R = H) and its *3′-methoxy*-derivative (V; R = OMe) in the following manner: 2-methoxyphenylacetonitrile, *2-benzyloxyphenylacetonitrile*, and 2 : 3-dimethoxyphenylacetonitrile were prepared from 2-methoxy-, 2-benzyloxy-, and 2 : 3-dimethoxy-benzaldehyde, respectively, according to Robertson (J., 1933, 489) through the stages of azlactone, pyruvic acid, and pyruvic acid oxime. Condensation of the above nitriles with ββ′-dichlorodiethylmethylamine gave *4-(2′-methoxyphenyl)-1-methylpiperidine-4-nitrile*, the corresponding *benzyloxy*-compound and *4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine-4-nitrile*. Hydrolysis of the benzyloxy-compound with hydrochloric acid and of the dimethoxy-compound with concentrated hydrobromic acid yielded the *iso*coumaranones (V; R = H and R = OMe).

We failed to prepare the desired corresponding coumarans (cf. VI) by the action of alkylmagnesium halides on these lactones. We were, however, partly successful when *4-acetyl-4-(2′-methoxyphenyl)-1-methylpiperidine*, from 4-(2′-methoxyphenyl)-1-methylpiperidine-4-nitrile with methylmagnesium iodide (cf. Winthrop Chem. Co., U.S.P. 2,248,018, 1941; *Chem. Abstr.*, 1941, **35**, 6394), was reduced with sodium and alcohol, and the crude product treated with concentrated hydrobromic acid. The basic oil thus formed gave a *picrate* whose analysis indicated that the desired coumaran (VI; R = H, R′ = Me) had been synthesised. Reduction of 4-acetyl-4-phenyl-1-methylpiperidine readily yielded *4-phenyl-4-(α-hydroxyethyl)-1-methylpiperidine*. On the other hand, attempts to prepare a ketone from 4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine-4-nitrile were completely unsuccessful.

When we tried to prepare primary amines directly from 4-arylpiperidine-4-nitriles with the aim of eventually obtaining coumarans, the action of sodium and alcohol eliminated the nitrile group in every case, giving 4-arylpiperidines. 4-Phenyl-1-methylpiperidine-4-nitrile gave 4-phenyl-1-methylpiperidine, identical with the product obtained by decarboxylation of 4-phenyl-1-methylpiperidine-4-carboxylic acid (cf. Eisleb, *loc. cit.*). 4-(2′-Benzyloxyphenyl)-1-methylpiperidine-4-nitrile yielded *4-(2′-hydroxyphenyl)-1-methylpiperidine* by simultaneous removal of the benzyl group, and 4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine-4-nitrile gave *4-(2′ : 3′-dimethoxyphenyl)-1-methylpiperidine*, which on hydrolysis with concentrated hydrobromic acid gave the *dihydroxy*-compound. That this elimination of the nitrile group is not confined to tertiary arylpiperidine nitriles was shown by the formation of *γ-phenyl-n-amyldiethylamine* from *γ-diethylamino-α-phenyl-α-ethylbutyronitrile*, prepared by condensation of α-phenylbutyronitrile with β-chloroethyldiethylamine.

Catalytic hydrogenation of 4-phenyl-1-methylpiperidine-4-nitrile yielded mainly *bis-(4-phenyl-1-methylpiperidyl-4-methyl)amine*, m. p. 91—93°.

The results of the pharmacological tests of some of the above compounds will be published elsewhere.

Experimental.

β-Dimethylamino-2-acetoxy-4-methoxypropiophenone Hydrochloride (VII; R = Ac).—Acetylpæonol (12·5 g.), paraformaldehyde (2·4 g.), and dimethylamine hydrochloride (5·4 g.) in ethyl alcohol (15 c.c.) were refluxed for 1 hour. More paraformaldehyde (1·0 g.) was then added, and the refluxing continued for 1 hour. On cooling, the *hydrochloride* of *β-dimethylamino-2-acetoxy-4-methoxypropiophenone* separated as a crystalline mass (10·1 g.), and a further 1·2 g. separated on addition of acetone (20 c.c.) and ether (100 c.c.) to the mother-liquors. When crystallised from ethyl alcohol, it had m. p. 175° (Found: C, 55·9; H, 6·9. $C_{14}H_{20}O_4NCl$ requires C, 55·8; H, 6·7%).

β-Dimethylamino-2-hydroxy-4-methoxypropiophenone Hydrochloride (VII; R = H).—The above acetyl derivative (5·0 g.) was refluxed for 1 hour with aqueous hydrochloric acid (15 c.c.). The solution was then evaporated to dryness in a vacuum, the residue taken up in hot alcohol, and ether added, whereupon the *hydrochloride* of (VII; R = H) was precipitated as a white solid. After crystallisation from alcohol–ethyl acetate, it had m. p. 166—167°. It gave a deep red coloration with ferric chloride (Found: C, 55·3; H, 7·0; N, 5·3. $C_{12}H_{16}O_3NCl$ requires C, 55·6; H, 6·9; N, 5·4%).

β-Piperidino-2-hydroxy-4-methoxypropiophenone Hydrochloride.—A mixture of pæonol (1·0 g.), paraformaldehyde (0·5 g.), and piperidine hydrochloride (0·8 g.) in alcohol (3 c.c.) was refluxed for 6 hours. After cooling, ether was added, and the resulting oily precipitate solidified on standing. The solid (1·4 g.) was filtered off, and after crystallisation from ethyl acetate–alcohol, the *hydrochloride* of *β-piperidino-2-hydroxy-4-methoxypropiophenone* was obtained in colourless needles, m. p. 188—189° (Found: C, 60·1; H, 7·3; N, 4·3. $C_{15}H_{22}O_3NCl$ requires C, 60·0; H, 7·3; N, 4·7%).

Reaction of β-Dimethylamino-2-hydroxy-4-methoxypropiophenone with Bromoacetophenone.—The base hydrochloride (2·6 g.) was dissolved in a solution of potassium hydroxide (1·12 g.) in water (3 c.c.), and a solution of bromoacetophenone (2·0 g.) in alcohol (16 c.c.) added. The mixture was boiled for 3 hours, alcohol removed, and the residue poured into dilute sodium hydroxide. After extraction with ether, the extract was washed with water, dried over sodium sulphate, and evaporated. The residue was again taken up in dry ether, and alcoholic hydrogen chloride added, precipitating a hydrochloride, m. p. 173—174° after crystallisation from ethyl acetate–alcohol. This showed no depression in m. p. on admixture with an authentic specimen of the hydrochloride of β-dimethylaminoacetophenone (m. p. 173—174°)

prepared from bromoacetophenone and dimethylamine. The material soluble in sodium hydroxide was precipitated as a dark oil by passing carbon dioxide into the solution. This was extracted with ether, the extract dried over sodium sulphate, and the ether distilled. A viscous phenolic oil remained, which on treatment with 2 : 4-dinitrophenylhydrazine gave a product, m. p. 244—245°, apparently the 2 : 4-*dinitrophenylhydrazone* of 2-hydroxy-4-methoxyphenyl vinyl ketone (Found : C, 53·8; H, 3·8; N, 16·7. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9; N, 15·7%).

Ethyl 2-β-Dimethylaminopropionyl-5-methoxyphenoxyacetate (VII; R = $CH_2{\cdot}CO_2Et$).—A mixture of ethyl 5-methoxy-2-acetylphenoxyacetate (3·75 g.; prepared from pæonol and bromoacetic ester), paraformaldehyde (1·0 g.), dimethylamine hydrochloride (1·25 g.), and alcohol (4 c.c.) was refluxed for 1 hour, more paraformaldehyde (0·25 g.) then being added and the refluxing continued for a further hour. After cooling, a little ether was added, and the *hydrochloride* of (VII; R = $CH_2{\cdot}CO_2Et$) separated as a white crystalline mass; recrystallised from ethyl acetate–alcohol, it had m. p. 149° (Found : C, 54·7; H, 6·9. $C_{16}H_{24}O_5NCl$ requires C, 55·6; H, 6·9%).

The corresponding *piperidino*-compound, prepared in the same manner, separated from alcohol–ethyl acetate in colourless prisms, m. p. 134° (Found : C, 59·2; H, 7·1; N, 3·5. $C_{19}H_{28}O_5NCl$ requires C, 59·2; H, 7·3; N, 3·6%).

2-β-Dimethylaminopropionyl-5-methoxyphenoxyacetic acid (VII; R = $CH_2{\cdot}CO_2H$).—Repetition of the above experiment but with the acid in place of the ester, gave the *hydrochloride* of (VII; R = $CH_2{\cdot}CO_2H$) in good yield. Crystallisation from alcohol gave colourless needles, m. p. 197° (Found : C, 53·1; H, 6·3; N, 3·9. $C_{14}H_{20}O_5NCl$ requires C, 53·0; H, 6·3; N, 4·3%).

The corresponding *piperidino*-compound melted at 183—184° after crystallisation from alcohol (Found : C, 57·4; H, 6·8; N, 3·7. $C_{17}H_{24}O_5NCl$ requires C, 57·1; H, 6·7; N, 3·9%).

Reaction of Ethyl 2-β-Dimethylamino-5-methoxyphenoxyacetate with Acetic Anhydride and Sodium Acetate.—When the hydrochloride of (VII; R = $CH_2{\cdot}CO_2Et$) (0·5 g.) was refluxed with acetic anhydride (5 c.c.) and sodium acetate (1·5 g.) for 45 minutes and the resulting solution worked up, only a nitrogen-free solid (m. p. 112°) could be isolated. The reaction also failed when (VII; R = $CH_2{\cdot}CO_2H$) was treated in the same manner.

α-Bromo-β-dimethylamino-2-acetoxy-4-methoxypropiophenone Hydrobromide.—To a solution of β-dimethylamino-2-acetoxy-4-methoxypropiophenone hydrochloride (4·5 g.) in glacial acetic acid (40 c.c.), warmed to 40°, was added dropwise with stirring during 1 hour a solution of bromine (2·4 g.) in acetic acid (20 c.c.). The acetic acid was then distilled under reduced pressure, leaving a viscous oil which was washed with ether. On addition of a little alcohol this formed a solid, white mass (6·2 g.) of the required compound, which formed plates from alcohol, m. p. 161° (Found : C, 40·2; H, 4·9; N, 3·7; Br, 36·7. $C_{14}H_{19}O_4NBr_2$ requires C, 39·6; H, 4·5; N, 3·3; Br, 37·7%).

The above *acetyl* compound was hydrolysed by heating for three hours with an equal amount of 50% hydrobromic acid in about 20 parts of 95% alcohol. Addition of ether then precipitated the *hydrobromide* of the *hydroxy*-compound as a white solid, obtained as needles, m. p. 179°, from alcohol and giving a deep red coloration with ferric chloride (Found : C, 38·2; H, 4·5; Br, 41·0. $C_{12}H_{17}O_3NBr_2$ requires C, 37·6; H, 4·4; Br, 41·7%).

Hydrochloride of 2-Dimethylaminomethyl-6-methoxycoumaranone (III; R = OMe, R′ = H).—The foregoing hydrobromide (1·0 g.) was mixed with powdered potassium carbonate (8·0 g.) and boiled with acetone (20 c.c.) for 1—2 minutes. The acetone solution was filtered, the carbonate washed with ether (20 c.c.), and the washings added to the filtrate. Addition of alcoholic hydrogen chloride then precipitated the hydrochloride of (III; R = OMe, R′ = H) as a white crystalline solid (0·4 g.), m. p. 144—145°. The product gave a very faint coloration with ferric chloride, showing the presence of traces of starting material. Attempts to crystallise it, however, resulted in polymerisation, with production of a *substance* with an indefinite m. p. (Found : C, 54·9; H, 5·8; N, 4·6. $C_{12}H_{16}O_3NCl$ requires C, 55·9; H, 6·2; N, 5·4%). The *picrate*, prepared by addition of aqueous picric acid to a solution of the hydrochloride, separated in needles, m. p. 123—124°, which, however, decomposed on attempted recrystallisation (Found : N, 11·6. $C_{18}H_{18}O_{10}N_4$ requires N, 12·4%).

7-Methoxy-2-acetylcoumarone.—*o*-Vanillin (20 g.) in water (30 c.c.) containing potassium hydroxide (7·4 g.), chloroacetone (12 g.), and absolute ethanol (150 c.c.) were refluxed for 4 hours. After cooling, water was added until no more oily precipitate was formed. This was extracted with ether, and the ether dried and evaporated. The residue, recrystallised from ethanol or light petroleum (b. p. 60—80°), formed colourless, soft needles, m. p. 92°; yield 10 g. (Found : C, 69·4; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

2-β-Piperidinopropionyl-7-methoxycoumarone Hydrochloride (IV).—The above coumarone (6 g.) was mixed with paraformaldehyde (2 g.), piperidine hydrochloride (4·5 g.), and absolute ethanol (10 c.c.) and refluxed for 6 hours. The solution was left overnight, then treated with acetone and ether, a solid being precipitated. This was dissolved in water, and when concentrated sodium carbonate solution was added an oil was formed which was extracted with ether. After drying, the solvent was removed. As the base decomposed when distillation was attempted in a high vacuum, the substance after removal of low-boiling bases in a vacuum desiccator (yield *ca.* 6 g.) was transformed into a *hydrochloride* in the usual manner; m. p. 170—172° from absolute alcohol (Found : N, 4·3. $C_{17}H_{22}O_3NCl$ requires N, 4·3%). When the base (1·38 g.), regenerated from the hydrochloride, was submitted to catalytic hydrogenation in absolute methanol (45 c.c.) in presence of platinic oxide (0·2 g.), 135 c.c. of hydrogen were taken up very slowly (1 mol. of hydrogen requires 120 c.c.). As the hydrochloride did not crystallise properly, a *picrate* was formed, m. p. 158—159° after crystallisation from water (Found : C, 53·3; H, 5·4. $C_{23}H_{26}O_{10}N_4$ requires C, 53·3; H, 5·0%).

Azlactone of 2-Benzyloxybenzaldehyde.—A mixture of 2-benzyloxybenzaldehyde (10 g.), hippuric acid (14 g.), sodium acetate (15 g.), and acetic anhydride (50 c.c.) was heated on the steam-bath for 1 hour, and the *azlactone* formed isolated by addition of ethyl alcohol (125 c.c.) and water (150 c.c.), and cooling; recrystallised from alcohol, it had m. p. 167—169° (Found : N, 3·9. $C_{23}H_{17}O_3N$ requires N, 3·9); yield 63%.

2-Benzyloxyphenylpyruvic Acid.—The above azlactone (10 g.) was refluxed with 10% aqueous sodium hydroxide (100 c.c.) for 5 hours in nitrogen, water (250 c.c.) was added, and the cooled solution saturated with sulphur dioxide. The precipitated benzoic acid was filtered off, the filtrate extracted twice with ether, boiled to remove ether, acidified to Congo-red with hydrochloric acid (20%), boiled to remove sulphur dioxide, and cooled in the ice chest. The *pyruvic acid* which separated, crystallised from 50% aqueous acetic acid, had m. p. 119—120° (Found : C, 71·0; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%); yield 70%.

2-Benzyloxyphenylacetonitrile.—The above acid was converted into its oxime by dissolving it (3 g.) in 10% aqueous sodium hydroxide (30 c.c.), adding hydroxylamine hydrochloride (3 g.), heating it at 50° for 5 minutes, and 24 hours later acidifying the mixture with hydrochloric acid. The crude oxime (3·2 g.) was not purified, but after being dried it was warmed with acetic anhydride (5 c.c.) until evolution of carbon dioxide had ceased, and the solution was poured into ice. The ethereal extract was washed free from acid with water, dried, and concentrated. Crystallised from light petroleum (b. p. 60—80°), the *nitrile* had m. p. 75—77° (Found : N, 6·2. $C_{15}H_{13}ON$ requires N, 6·3%); yield 90%.

The *azlactone* of 2-methoxybenzaldehyde was prepared from the aldehyde (18 g.), hippuric acid (20·6 g.), sodium acetate (9·5 g.), and acetic anhydride (74 c.c.); recrystallised from alcohol, it had m. p. 154—156° (Found : N, 5·0. $C_{17}H_{13}O_3N$ requires N, 5·0%). When this was hydrolysed exactly as described for the benzyloxy-compound, it yielded the crude pyruvic acid, the oxime of which, without purification, was treated with acetic anhydride and gave 2-methoxyphenylacetonitrile, m. p. 66—69° (cf. Pschorr *et al.*, *Ber.*, 1900, **33**, 162).

The *azlactone* of 2 : 3-dimethoxybenzaldehyde was prepared from the aldehyde (8·39 g.), hippuric acid (9 g.), acetic anhydride (32 c.c.), and sodium acetate (4·1 g.), and after crystallising from ethyl alcohol had m. p. 167—168° (Found : N, 4·3. $C_{18}H_{15}O_4N$ requires N, 4·5%). From this azlactone, 2 : 3-dimethoxybenzyl cyanide (cf. Montequi, *Anal. Soc. Fis. Quim.*, 1929, **27**, 692) was prepared in the following manner. The azlactone (5 g.) was boiled with 10% aqueous sodium hydroxide (50 c.c.) for 5 hours in nitrogen, the solution cooled to 50°, and hydroxylamine hydrochloride (3 g.) added. After 24 hours, excess of dilute hydrochloric acid was added, and the precipitated mixture of oxime and benzoic acid was dried, warmed with acetic anhydride (10 c.c.) until evolution of carbon dioxide had ceased, and decomposed with ice water; the ethereal extract of the nitrile was washed free from acid with dilute sodium carbonate solution, dried, and concentrated. The pure *nitrile* had b. p. 158—160°/12 mm. (Found : N, 7·5. $C_{10}H_{11}O_2N$ requires N, 7·9%).

4-(2′-*Benzyloxyphenyl*)-1-*methylpiperidine*-4-*nitrile Hydrochloride*.—Powdered sodamide (2·8 g.) was added to a solution of 2-benzyloxyphenylacetonitrile (7·1 g.) and ββ′-dichlorodiethylamine (5 g.) in toluene (30 c.c.) at room temperature with stirring, and the reaction completed by refluxing for one hour. After addition of water to the cooled solution, the mixture was extracted with ether. The ether–toluene solution was extracted with dilute hydrochloric acid, and the extract washed with ether, and made alkaline with dilute sodium hydroxide solution. The precipitated base was extracted with ether, and after removal of the ether the base was purified by warming with light petroleum (b. p. 100—120°), the impurities remaining undissolved. On passing dry hydrogen chloride into this solution, the *hydrochloride* of the base was formed. Recrystallised from ethyl alcohol–ethyl acetate, it had m. p. 220—221° (Found : C, 69·8; H, 6·5. $C_{20}H_{23}ON_2Cl$ requires C, 70·1, H, 6·7%).

Hydrochloride of 4-(2′-*Hydroxyphenyl*)-1-*methylpiperidine*-4-*carboxylic Acid Lactone* (V; R = H).—The above hydrochloride (4 g.) was heated with concentrated hydrochloric acid (24 c.c.) in a sealed tube at 120—130° for 5 hours. After cooling, water was added, and the aqueous solution extracted with ether, and made alkaline with dilute sodium carbonate solution; a base was liberated, the dry ethereal solution of which gave a crystalline *hydrochloride* with ethyl-alcoholic hydrogen chloride. It was purified by sublimation at 200°/0·2 mm. and had m. p. 260—263°. When kept free from moisture the hydrochloride retained this m. p., but on exposure to the atmosphere, the m. p. fell to *ca.* 180°, at which temperature a gas was given off and the original hydrochloride, m. p. 260—263°, was re-formed (Found : C, 59·7; H, 6·6; N, 5·1. $C_{13}H_{16}O_2NCl,\frac{1}{2}H_2O$ requires C, 59·4; H, 6·5; N, 5·3%).

4-(2′ : 3′-*Dimethoxyphenyl*)-1-*methylpiperidine*-4-*nitrile*.—2 : 3-Dimethoxyphenylacetonitrile (8 g.) and ββ′-dichlorodiethylmethylamine (7 g.) were condensed in toluene (50 c.c.) at 80° by the gradual addition of sodamide (4 g.) with stirring, followed by refluxing for 1 hour. On being worked up in the previously described manner, the *nitrile* was obtained as a crystalline solid (m. p. 107—110°) after distillation at 155—157°/0·06 mm. (Found : C, 69·7; H, 7·5; N, 10·8. $C_{15}H_{20}O_2N_2$ requires C, 69·3; H, 7·7; N, 10·8%). The picrate, crystallised from alcohol, had m. p. 194—196°.

4-(2′-*Hydroxy*-3′-*methoxyphenyl*)-1-*methylpiperidine*-4-*carboxylic Acid Lactone* (V; R = OMe).—The above nitrile (2 g.) in hydrobromic acid (*d* 1·3; 20 c.c.) was heated in a nitrogen-filled sealed tube at 120° for 5 hours. On cooling a crystalline hydrobromide separated. It was sublimed in a high vacuum and had m. p. 265—270°. The free *lactone* was obtained by shaking this hydrobromide with a mixture of ether and dilute sodium carbonate solution, and treating the ethereal solution with diazomethane to methylate a small amount of phenolic by-product. Recrystallised from light petroleum (b. p. 60—80°), it had m. p. 115—117° (Found : C, 68·2; H, 6·7; N, 5·9; OMe, 11·5. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7; OMe, 12·5%).

4-(2′-*Methoxyphenyl*)-1-*methylpiperidine*-4-*nitrile*.—Powdered sodamide (12 g.) was gradually added with stirring to a solution of 2-methoxyphenylacetonitrile (22 g.) and ββ′-dichlorodiethylmethylamine (24 g.) in toluene (50 c.c.) at 80°, and the mixture refluxed for 2 hours. On being worked up as previously described, the product was obtained crystalline from light petroleum (b. p. 60—80°); m. p. 97—99° (Found : C, 72·7; H, 8·1; N, 12·1. $C_{14}H_{18}ON_2$ requires C, 72·9; H, 7·8; N, 12·1%). The picrate from alcohol, had m. p. 250°.

4-*Acetyl*-4-(2′-*methoxyphenyl*)-1-*methylpiperidine*.—A solution of methylmagnesium iodide in benzene (50 c.c.) was prepared from magnesium (2 g.) and methyl iodide (11·4 g.), the ether and excess of methyl iodide being removed by distillation, and to the filtered solution was added 4-(2′-methoxyphenyl)-1-methylpiperidine-4-nitrile (4·6 g.), and the mixture refluxed for 16 hours. A little ice and 20% sulphuric acid (20 c.c.) were then added, and the aqueous acid layer made alkaline with aqueous sodium hydroxide; the ketone was thus obtained as an oil, whose *picrate*, recrystallised from alcohol, had m. p. 197—200° (Found : N, 11·9. $C_{21}H_{24}O_9N_4$ requires N, 11·8%). The oxime, from aqueous methanol, had m. p. 150—153°.

4-*Phenyl*-4-(*α-hydroxyethyl*)-1-*methylpiperidine*.—4-Acetyl-4-phenyl-1-methylpiperidine (2 g.) was dissolved in absolute alcohol (50 c.c.), and sodium (4 g.) slowly added. The reaction was completed by heating for 2 hours at 120° under reflux. Some of the alcohol was then distilled off, and the residue treated with water and extracted with ether, which on drying and evaporating left the secondary *alcohol*; after crystallising from light petroleum (b. p. 80—100°) this had m. p. 117—119° (Found : N, 6·6; $C_{14}H_{21}ON$ requires N, 6·4%). The acetate, prepared by treatment of the alcohol with acetic anhydride in pyridine, was an oil, b. p. 113—115°/0·1 mm.

2-*Methyl*-3-4′-spiro-(1′-*methylpiperidine*)*coumaran* (VI; R = H; R′ = Me).—4-Acetyl-4-(2′-methoxyphenyl)-1-methylpiperidine (2·8 g.) was dissolved in absolute alcohol (60 c.c.), sodium (4·8 g.) gradually added, and the solution finally heated at 120° for 2 hours; most of the alcohol was then distilled off, water added, and the precipitated oil extracted with ether. It did not give any crystalline derivatives. The crude alcohol (2·3 g.) was heated in a pressure bottle with hydrobromic acid (*d* 1·7; 10 c.c.) at 120° for 5 hours. On being made alkaline with sodium hydroxide solution and then extracted with ether, this afforded an oil (1 g.), b. p. *ca.* 150°/0·2 mm. It gave a *picrate*, m. p. 182—184° (Found : N, 13·0. $C_{20}H_{22}O_8N_4$ requires N, 12·6%).

4-*Phenyl*-1-*methylpiperidine*.—Sodium (2·8 g.) was added gradually to a solution of 4-phenyl-1-methylpiperidine-4-nitrile (2 g.) in absolute alcohol (34 c.c.) and the solution heated at 130° for 30 minutes; more sodium (1 g.) and alcohol (10 c.c.) were then added, and heating at 130° continued for further 150 minutes. The mixture was poured into water and extracted with ether; the oil (1·5 g.) obtained had b. p. 120—122°/10 mm. This formed a *picrate* which, crystallised from alcohol, had m. p. 239—240°, alone or mixed with the picrate of 4-phenyl-1-methylpiperidine (m. p. 239—240°), prepared by decarboxylation of 4-phenyl-1-methylpiperidine-4-carboxylic acid (cf. B.P. 501,135) (Found : C, 54·2; H, 5·0; N, 13·4. $C_{18}H_{20}O_7N_4$ requires C, 53·5; H, 5·0; N, 13·9%).

4-(2′-*Hydroxyphenyl*)-1-*methylpiperidine*.—4-(2′-Benzyloxyphenyl)-1-methylpiperidine-4-nitrile (3·1 g.) was reduced with sodium (2·5 g.) and absolute alcohol (25 c.c.) as previously described, and after addition of water to the reaction mixture, the solution was neutralised (phenolphthalein) with dilute hydrochloric acid; 4-(2′-*hydroxyphenyl*)-1-*methylpiperidine* was precipitated as a solid which, crystallised from benzene, had m. p. 179—181° (Found : C, 75·6; H, 8·8; N, 7·5. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%).

4-(2′ : 3′-*Dimethoxyphenyl*)-1-*methylpiperidine*.—4-(2′ : 3′-Dimethoxyphenyl)-1-methylpiperidine-4-nitrile (2·6 g.) on reduction with sodium (5 g.) and absolute alcohol (30 c.c.) gave the above *piperidine* as a colourless liquid, b. p. 125—127°/1 mm. (Found : N, 6·9. $C_{14}H_{21}O_2N$ requires N, 6·0%). The *picrate*, from alcohol, had m. p. 159—162° (Found : N, 11·7. $C_{20}H_{22}O_9N_4$ requires N, 12·1%).

4-(2′ : 3′-*Dihydroxyphenyl*)-1-*methylpiperidine*.—The above piperidine (1·2 g.) in 66% hydrobromic acid (10 c.c.)

and acetic acid (5 c.c.) was heated under reflux for 4 hours and then made alkaline with sodium carbonate solution. A little sodium hydrosulphite was added, and the solution extracted with ether, the *dihydroxy*-compound being obtained as a white solid which, crystallised from benzene–alcohol, had m. p. 200—205° (Found: C, 69·4; H, 8·3; N, 6·6. $C_{13}H_{17}O_2N$ requires C, 69·6; H, 8·2; N, 6·8%).

γ-Diethylamino-α-phenyl-α-ethylbutyronitrile was prepared by condensing α-phenylbutyronitrile (8 g.) with β-chloroethyldiethylamine (8·6 g.) in dry toluene (50 c.c.), powdered sodamide (2·7 g.) being added gradually with stirring, and the reaction completed by heating at 130—140° under reflux for one hour. Isolated in the usual way, it was obtained as a colourless oil, b. p. 161—166°/10—12 mm. (Found: N, 11·0. $C_{16}H_{24}N_2$ requires N, 11·4%); yield 9 g.

γ-Phenyl-n-amyldiethylamine, formed when the above nitrile (3 g.) was reduced with sodium (4 g.) and absolute alcohol (30 c.c.) as previously described, is a colourless oil, b. p. 134°/15 mm. (Found: N, 7·0. $C_{15}H_{25}N$ requires N, 6·4%).

Bis-(4-phenyl-1-methylpiperidyl-4-methyl)amine.—4-Phenyl-1-methylpiperidine-4-nitrile (3 g.), dissolved in absolute alcohol (40 c.c.), was hydrogenated in presence of charcoal (2 g.) and 5% aqueous palladium chloride (5 c.c.), three further 5-c.c. portions of the latter being added during the hydrogenation. When the hydrogen uptake had ceased, the alcoholic solution was freed from catalyst, concentrated to small bulk, excess sodium hydroxide solution added, and the liberated base taken up in ether. The secondary *amine* distilled at 160—170°/0·05 mm.; recrystallised from light petroleum (b. p. 60—80°), it had m. p. 90—93° (Found: C, 80·0; H, 9·6; N, 10·4. $C_{26}H_{32}N_2$ requires C, 79·8; H, 9·5; N, 10·7%).

RESEARCH DEPARTMENT, ROCHE PRODUCTS LTD., WELWYN GARDEN CITY. [*Received, January 5th*, 1944.]

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69. *Synthetic Analgesics. Part II. A New Synthesis of Pethidine and Similar Compounds.**

By F. BERGEL, A. L. MORRISON, and H. RINDERKNECHT.

A new method of synthesising 4-arylpiperidine-4-nitriles is described. Arylacetonitriles were condensed with 2 mols. of β-chloroethyl vinyl ether, and the resulting αα-bis-(β′-vinyloxyethyl)arylacetonitriles hydrolysed to the corresponding di-alcohols, which were chlorinated and then treated with primary amines to give the above nitriles. The same di-alcohols were obtained by hydrolysis of αα-bis-(β′-alkoxymethyloxyethyl)arylacetonitriles, which were prepared by condensation of arylacetonitriles with 2 mols. of alkyl-β-chloroethylformals.

In this way, 4-phenyl-1-methylpiperidine-4-nitrile and 4-o-*tolyl*-1-*methylpiperidine-4-nitrile* were prepared. Hydrolysis with concentrated hydrochloric acid gave the corresponding carboxylic acids. Several esters of 4-phenyl-1-methylpiperidine-4-carboxylic acid have been prepared. The ethyl ester was also obtained by direct alcoholysis of the nitrile.

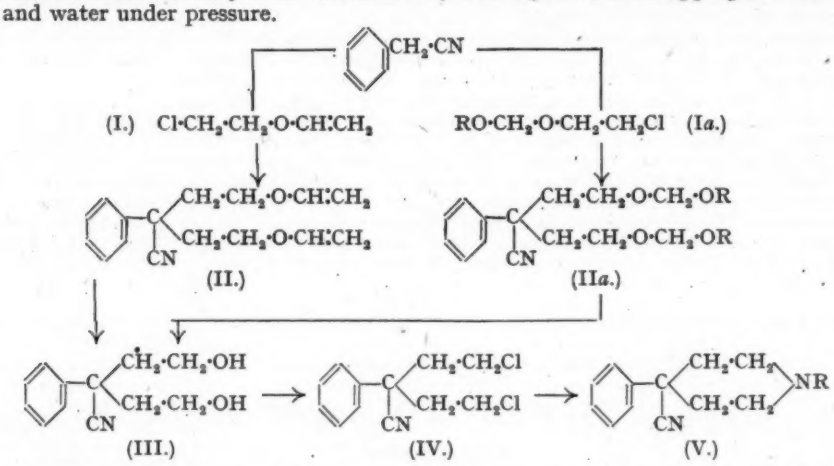
CONDENSATION of phenylacetonitrile with alkyl halides and alkylene dihalides, in the latter case to give phenyl-*cyclo*paraffin nitriles, in presence of sodamide was described by Bodroux and Taboury (*Compt. rend.*, 1910, **150**, 1241, etc.) and Case (*J. Amer. Chem. Soc.*, 1934, **56**, 715). Eisleb later (*Ber.*, 1941, **75**, 1435) reported the synthesis of heterocyclic compounds by the condensation of phenylacetonitriles with ββ′-dihalogenoethylalkylamines, ethers, and sulphides. In view of the pronounced vesicant nature of ββ′-dihalogenoethylmethylamine, we looked for another method of preparing 4-arylpiperidine-4-nitriles, which are intermediates of important analgesics. One of the alternative methods considered was the preparation of αα-bis-(β′-halogenoethyl)arylacetonitriles which, on condensation with primary amines, would give the desired piperidine nitriles. Attempts to prepare such dihalogeno-compounds by condensation of phenylacetonitriles with 2 mols. of chlorobromoethane were unsuccessful, *cyclo*propane derivatives being the main products. Although ethylene chlorohydrin may be condensed with the sodio-derivative of phenylacetonitrile (Knowles and Cloke, *J. Amer. Chem. Soc.*, 1932, **54**, 2028), the introduction of a second hydroxyethyl group was found to be impossible. The use of β-halogenoethyl alkyl ethers gave products which could not be converted into the desired dihalogenonitriles, as the agent used for fission of the ether linkage also hydrolysed the nitrile group to the carboxylic acid, the resulting product being a derivative of α-phenylbutyrolactone, which was of no use for the projected syntheses. We finally achieved our aim by condensation of phenylacetonitrile in presence of sodamide with 2 mols. of β-chloroethyl vinyl ether (I) to give *αα-bis-(β′-vinyloxyethyl)phenylacetonitrile* (II), which on mild acid hydrolysis yielded *αα-bis-(β′-hydroxyethyl)phenylacetonitrile* (III) (cf. Cretcher, Koch, and Pittenger, *ibid.*, 1925, **47**, 3083). The same dialcohol was also obtained by mild acid hydrolysis of *αα-bis-(β′-methoxymethyloxyethyl)phenylacetonitrile* (II*a*; R = Me), formed by condensation of phenylacetonitrile with 2 mols. of *methyl-β-chloroethylformal* (I*a*; R = Me) in presence of sodamide. This di-alcohol on treatment with thionyl chloride in presence of diethylaniline yielded *αα-bis-(β′-chloroethyl)phenylacetonitrile* (IV), which, when condensed with primary amines such as methylamine or benzylamine in aqueous-alcoholic solution, gave 1-alkyl- or 1-aralkyl-4-phenylpiperidine-4-nitriles (V). 4-Phenyl-1-methylpiperidine-4-nitrile thus prepared possessed all the properties described by Eisleb (*loc. cit.*).

The above β-chloroethylalkylformals were more readily prepared by the action of ethylene oxide on chloromethyl ethers at low temperature (cf. Blanchard, *Bull. Soc. chim.*, 1936, **39**, 1263) than by the methods suggested in the literature (Henry, *Ber.*, 1895, **28**, Ref. 851).

The hydrolysis of 4-phenyl-1-methylpiperidine-4-nitrile to the corresponding carboxylic acid was easily achieved by boiling with concentrated hydrochloric acid. In addition to the ethyl ester (pethidine) and those esters mentioned by Schaumann (*Arch. Path. Exp. Pharm.*, 1940, **196**, 109), we have prepared the n-*propyl*,

* Cf. B.PP. 550,963 (1943), 550,970 (1943), and 556,976 (1943).

iso*propyl*, β-*hydroxyethyl*, cyclo*hexyl* and *allyl* esters of 4-phenyl-1-methylpiperidine-4-carboxylic acid. The ethyl ester was also obtained directly from the nitrile by heating it with an appropriate mixture of alcohol, sulphuric acid, and water under pressure.



We also synthesised 4-o-*tolyl*-1-*methylpiperidine*-4-*nitrile*, the corresponding *carboxylic acid*, and its *ethyl* ester, according to the above method.

The results of pharmacological tests of the above compounds, obtained in association with Professor A. D. Macdonald and Dr. G. Woolfe, University of Manchester (Department of Pharmacology), will be published elsewhere.

Experimental.

Methyl-β-chloroethylformal (I*a*; R = CH_3).—Chloromethyl methyl ether (80 g.) was added slowly with stirring to mercuric chloride (0·6 g.) in dry liquid ethylene oxide (44 g.), the temperature being maintained at −10° by external cooling. After standing at room temperature overnight, the colourless product was washed with dilute sodium carbonate solution and water, dried over anhydrous potassium carbonate, and distilled. The *formal* was a colourless liquid, b. p. 134—139° (Found: Cl, 25·2. $C_4H_9O_2Cl$ requires Cl, 28·5%); yield 78·5 g. It may be obtained pure by washing repeatedly with water (Found: Cl, 28·8%), but can be employed in the impure state for condensation with phenylacetonitrile.

β-Chloroethylethylformal (I*a*; R = Et), prepared in a similar manner (yield, 72%), was a colourless liquid, b. p. 62—65°/50 mm. (Found: Cl, 20·7. $C_5H_{11}O_2Cl$ requires Cl, 25·4%).

αα-Bis-(β′-vinyloxyethyl)phenylacetonitrile (II).—Phenylacetonitrile (431 g.) was added gradually with mechanical stirring to a suspension of powdered sodamide (317 g.) in a mixture of chloroethyl vinyl ether (867 g.) and dry benzene (4400 c.c.). The temperature of the reaction mixture was kept between 40° and 50° until all the nitrile had been added; it was then slowly raised to boiling point, and refluxing continued for 1 hour. The resulting product was poured into a large separating funnel and washed twice with water. The benzene was then distilled off, and the residue distilled in a high vacuum. The *nitrile* (730 g.) distilled at 125—135°/0·15 mm. as a colourless oil (Found: C, 73·9, 75·8; H, 7·4, 7·6; N, 6·4, 6·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%). It was difficult to effect complete separation from α-(β′-vinyloxyethyl)phenylacetonitrile, b. p. 110°/0·15 mm., formed as a by-product.

αα-Bis-(β′-methoxymethoxyethyl)phenylacetonitrile (II*a*; R = CH_3), prepared by condensation of phenylacetonitrile with β-chloroethylmethylformal (I*a*) in a similar manner, was obtained as a faintly yellow oil, b. p. 147—155°/0·05—0·1 mm. (Found: C, 66·0; H, 7·8; N, 4·9. $C_{16}H_{23}O_4N$ requires C, 65·6; H, 7·8; N, 4·8); yield 61%. The β′-ethoxy-homologue was obtained in an analogous manner from phenylacetonitrile and β-chloroethylethylformal as a slightly yellow oil, b. p. 167—169°/0·05 mm.; yield 77%.

αα-Bis-(β′-hydroxyethyl)phenylacetonitrile (III).—(A) αα-Bis-(β′-vinyloxyethyl)phenylacetonitrile (7·9 g.) was suspended in water (60 c.c.) and heated to 80° with vigorous stirring. Concentrated hydrochloric acid (2 c.c.) was then added, whereupon hydrolysis set in with evolution of acetaldehyde. After 10 minutes' stirring, on completion of the reaction, the mixture was cooled, and the aqueous layer separated from the oil. The oil soon solidified, and was recrystallised from ethyl acetate, chloroform, or water, the *di-alcohol* being obtained as a white crystalline powder. A further small quantity crystallised out from the aqueous part on cooling to 0°. Yield of crystalline material, 4·4 g.; m. p. 96—98° (Found: C, 70·3; H, 7·4; N, 6·7. $C_{12}H_{15}O_2N$ requires C, 70·3; H, 7·3; N, 6·8%).

(B) αα-Bis-(β′-ethoxymethoxyethyl)phenylacetonitrile (13 g.) was suspended in water (260 c.c.) and heated to 92°, concentrated hydrochloric acid (5·2 c.c.) then being added. Formaldehyde and ethyl alcohol were evolved. The mixture was kept at 90—92° for 20—25 minutes to complete hydrolysis. After cooling, the di-alcohol was extracted with ethyl acetate, from which it crystallised after evaporation of some solvent (yield 5·9 g.). It had m. p. 96—98° alone and when mixed with the product obtained in (A).

αα-Bis-(β′-chloroethyl)phenylacetonitrile (IV).—αα-Bis-(β′-hydroxyethyl)phenylacetonitrile (6·0 g.) was suspended in diethylaniline (12·0 g.), and thionyl chloride (12·0 g.) added dropwise with efficient stirring and cooling. The mixture was then warmed to 80° for 30 minutes, cooled to 40°, and poured into a mixture of ice water and ether with vigorous stirring. The ethereal layer was separated, washed with cold sodium hydroxide solution and water, dried over anhydrous sodium sulphate, and evaporated. The product distilled at 135—138°/0·1—0·2 mm. as a yellow oil (6·6 g.) which solidified on standing; m. p. 52°. The *nitrile* (IV) may also be purified by recrystallising from alcohol (Found: C, 59·8; H, 5·4; N, 5·8; Cl, 29·0. $C_{12}H_{13}NCl_2$ requires C, 59·5; H, 5·7; N, 5·6; Cl, 28·8%).

4-*Phenyl*-1-*methylpiperidine*-4-*nitrile* (V).—A mixture of αα-bis-(β′-chloroethyl)phenylacetonitrile (5·0 g.), alcohol (10 c.c.), and a 50% aqueous solution of methylamine (5·1 g.) was heated in a sealed tube at 145° for 17 hours. After cooling, the solvents were distilled off under reduced pressure, and the residue taken up in dilute hydrochloric acid. Non-basic material was removed by extraction with ether, the aqueous part made alkaline, and the liberated base extracted with ether. The extract was washed with water, dried over anhydrous sodium sulphate, and evaporated. The product distilled at 126°/0·5 mm. as a faintly yellow oil (3·4 g.), which solidified on standing, m. p. 53°. Its picrate

melted at 239—240° after recrystallisation from alcohol and gave no depression in m. p. when mixed with a sample obtained by Eisleb's method (*loc. cit.*) (Found: C, 53·5; H, 4·5; N, 15·9. Calc. for $C_{19}H_{19}O_7N_5$: C, 53·2; H, 4·4; N, 16·3%).

Ethyl 4-*Phenyl*-1-*methylpiperidine*-4-*carboxylate*.—A mixture of 4-phenyl-1-methylpiperidine-4-nitrile (20 g.), concentrated sulphuric acid (30 g., 98%), water (0·26 g.), ethanol (46 g.), and ammonium chloride (5·36 g.) was heated in an autoclave at 160° for 7 hours, then made alkaline with cold sodium hydroxide solution, and extracted with ether. After being washed and dried over anhydrous sodium sulphate, the extract was evaporated. The product distilled at 115°/0·2 mm. as a colourless oil (11·1 g.) and was identical with ethyl 4-phenyl-1-methylpiperidine-4-carboxylate obtained by successive hydrolysis of the nitrile and esterification of the acid. From the alkaline mother-liquor, 4-phenyl-1-methylpiperidine-4-carboxylic acid (6·5 g.) was recovered. n-*Propyl* 4-*phenyl*-1-*methylpiperidine*-4-*carboxylate hydrochloride* was prepared from the corresponding acid chloride hydrochloride and *n*-propyl alcohol according to Eisleb (*loc. cit.*); m. p. 181—183° (Found: Cl, 11·9. $C_{16}H_{24}O_2NCl$ requires Cl, 11·8%). The *isopropyl hydrochloride* had m. p. 192—195° (Found: Cl, 12·1. $C_{16}H_{24}O_2NCl$ requires Cl, 11·8%), and the *β-hydroxyethyl hydrochloride* m. p. 195—200° (Found: Cl, 11·6. $C_{15}H_{22}O_3NCl$ requires Cl, 12·0%).

The *allyl ester hydrochloride* had m. p. 155—158° (Found: N, 4·5; Cl, 11·3. $C_{16}H_{22}O_2NCl$ requires N, 4·8; Cl, 11·9%) [in the preparation of the free ester a mixture of allyl alcohol and pyridine (2 mols.) was added to the acid chloride hydrochloride in order to prevent addition of hydrogen chloride to the double bond of the allyl group]; and the cyclo*hexyl hydrochloride* had m. p. 234—236° (Found: C, 67·4; H, 8·5; N, 4·4; Cl, 10·7. $C_{19}H_{28}O_2NCl$ requires C, 67·6; H, 8·3; N, 4·2; Cl, 10·4%). The five foregoing hydrochlorides were recrystallised from alcohol–ether.

αα-Bis-(β′-vinyloxyethyl)-o-tolylacetonitrile.—Powdered sodamide (10 g.) was added in several portions to a solution of *o*-tolylacetonitrile (11 g.) and β-chloroethyl vinyl ether (39 g.) in dry toluene (80 c.c.), the temperature of the reaction mixture being maintained at about 40°. The reaction was completed by refluxing for 2 hours; the cooled reaction mixture was then poured into water, the toluene layer separated, washed with water, and evaporated under reduced pressure. The residue on distillation gave the *nitrile* as a yellowish oil, b. p. 135—140°/0·1 mm. (Found: N, 4·9. $C_{17}H_{21}O_2N$ requires N, 4·9%).

αα-Bis-(β′-hydroxyethyl)-o-tolylacetonitrile.—The foregoing nitrile was hydrolysed with dilute hydrochloric acid according to the method given above, the temperature being kept at 90°. On cooling, the *di-alcohol* crystallised in white needles; recrystallised from benzene, it had m. p. 95—100° (Found: C, 71·3; H, 7·8. $C_{13}H_{17}O_2N$ requires C, 71·3; H, 7·8%).

4-(*o-Tolyl*)-1-*methylpiperidine*-4-*nitrile*.—αα-Bis-(β′-hydroxyethyl)-*o*-tolylacetonitrile was treated with thionyl chloride as described above, and the crude dichloride used directly for the condensation with methylamine. Crude dichloride (5 g.) was heated with 33% aqueous solution of methylamine (11 c.c.) and alcohol (27 c.c.) in a sealed tube at 120—140° for 8 hours. The solvents were then removed under reduced pressure, and the residue taken up in 2N-hydrochloric acid (12·5 c.c.). On cooling, 4-(*o*-tolyl)-1-methylpiperidine-4-nitrile hydrochloride (4·0 g.) crystallised; m. p. 279—280°. The *picrate* had m. p. 265° (decomp.) (Found: C, 54·9; H, 5·3; N, 16·0. $C_{20}H_{21}O_7N_5$ requires C, 54·3; H, 4·8; N, 15·8%).

Ethyl 4-(o-*Tolyl*)-1-*methylpiperidine*-4-*carboxylate*.—The corresponding piperidine nitrile hydrochloride (4 g.) was heated at 130° with concentrated hydrochloric acid (16 c.c.) in a sealed tube for 5 hours. The reaction mixture was made alkaline with 4N-sodium hydroxide solution, and carbon dioxide passed through; the piperidine carboxylic acid (3 g.) was precipitated in white needles, m. p. 300—310° (decomp.). It was filtered off, dried over phosphoric oxide, and treated with thionyl chloride (8 c.c.). After refluxing for 15 minutes, the excess thionyl chloride was removed, and after addition of ethyl alcohol (8·6 c.c.) to the residue, the mixture was heated on the water-bath for 15 minutes and then filtered from insoluble material. After removal of solvent, the residual oil was distilled, to give the *ethyl ester*, b. p. 175°/11 mm., as a colourless oil (2·9 g.) (Found: C, 73·2; H, 8·6; N, 5·9. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·5%). The *hydriodide*, a white crystalline solid, had m. p. 175—176° (Found: I, 32·6. $C_{16}H_{24}O_2NI$ requires I, 32·6%).

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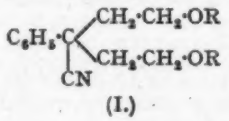
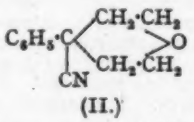
70. *Synthetic Analgesics. Part III. The Action of Hydrogen Halides on Ethers of αα-Bis-(β′-hydroxyethyl)phenylacetonitrile.**

By F. BERGEL, A. L. MORRISON, and H. RINDERKNECHT.

The action of hydrogen halides on various diethers of αα-bis-(β′-hydroxyethyl)phenylacetonitrile and on 4-phenyl-4-pentamethylene oxide-4-nitrile, and the resulting products are described. According to the strength and kind of hydrogen halide α-(*β′-hydroxyethyl*)-α-*phenylbutyrolactone*, α-(*β′-bromoethyl*)-α-*phenylbutyrolactone*, or *αα-bis-(β′-bromoethyl)phenylacetic acid* was formed. The ethyl ester of the last compound when condensed with methylamine gave ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (pethidine).

IN Part II (preceding paper) we described the selective hydrolysis of vinyl and alkoxymethyl ethers of αα-bis-(β′-hydroxyethyl)phenylacetonitrile (I, R = H) to the free di-alcohol, the nitrile group not being affected. We have now examined the products of acid hydrolysis of these ethers under more vigorous conditions and have included alkyl ethers and the cyclic ether 4-phenylpentamethylene oxide-4-nitrile (II), first prepared by Eisleb (cf. *Ber.*, **1941**, **74**, **1433**; U.S.P. 2,242,575). He stated that it may be converted into the corresponding piperidinecarboxylic acid, by hydrolysing the nitrile group with potassium hydroxide, then splitting the ether linkage with concentrated solutions of hydrogen halides to give dihalogenated acids which were then condensed with primary amines. No experimental details of these reactions are given, and the dihalogenated acids are described as oils.


(I.)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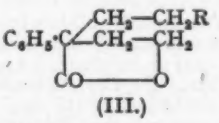
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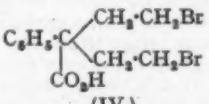

(IV.)

* Pend. Pat. Appl. 17,897, 1942.

αα-Bis-(β′-ethoxyethyl)phenylacetonitrile (I, R = Et), not hitherto described, was prepared by the condensation of phenylacetonitrile with 2 mols. of β-bromoethyl ethyl ether in presence of sodamide.

We did not attempt to hydrolyse the nitrile group in the above compounds with caustic alkali before treatment with hydrogen halide acids, for we had previously noticed that a similar hydrolysis (cf. Part II) proceeded smoothly under acid conditions.

On boiling with dilute hydrochloric acid, (I, R = $CH{:}CH_2$) and (I, R = $CH_2{\cdot}O{\cdot}CH_3$) yielded α-(β′-*hydroxyethyl*)-α-*phenylbutyrolactone* (III, R = OH). When treated with aqueous hydrogen bromide saturated at 0°, and heated in a sealed tube at 100—130°, (I, R = Et) gave as main product α-(β′-*bromoethyl*)-α-*phenylbutyrolactone* (III, R = Br): (I, R = OH), (I, R = $CH{:}CH_2$), and (I, R = $CH_2{\cdot}O{\cdot}CH_3$) would probably give the same product. In the case of (II), in order to prevent lactone formation, the crude hydrolysis product was not distilled but esterified with ethyl alcohol and then condensed with methylamine. No pethidine, however, could be isolated, which indicated that the original hydrolysis product consisted mainly of the bromolactone (III, R = Br).

We prepared *αα-bis-(β′-bromoethyl)phenylacetic acid* (IV) from all the above ethers and also from the dialcohol by heating with aqueous hydrogen bromide (saturated at −10°) in a sealed vessel at 120—130°. Contrary to Eisleb's findings (*loc. cit.*), this acid is a solid, m. p. 115—118°, which is rather unstable, turning oily on prolonged standing or heating, probably due to partial formation of (III, R = Br). Treatment with aqueous hydrogen chloride saturated at −20° under similar conditions yielded only traces of αα-bis-(β′-chloroethyl)acetic acid and gave mainly α-(β′-chloroethyl)-α-phenylbutyrolactone (III, R = Cl).

Esterification of (IV) with ethyl-alcoholic hydrogen chloride, followed by condensation with methylamine, yielded ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (pethidine).

When α-(β′-bromoethyl)-α-phenylbutyrolactone was condensed with piperidine it yielded α-(β′-*piperidinoethyl*)-α-*phenylbutyrolactone* (III, R = $C_5H_{10}N$).

Experimental.

αα-Bis-(β′-ethoxyethyl)phenylacetonitrile (I, R = Et).—Powdered sodamide (24 g.) was added in several portions with stirring to a solution of phenylacetonitrile (24 g.) and β-bromoethyl ethyl ether (92 g.) in dry toluene (150 c.c.), the temperature of the mixture being kept at 40—50°. The product was washed with water, the toluene distilled off under reduced pressure, and the product distilled in a high vacuum, to give the *nitrile*, b. p. 120—123°/0·05 mm., as a yellowish oil (29 g.) (Found: N, 5·8; OEt, 34·0. $C_{16}H_{23}O_2N$ requires N, 5·3; OEt, 34·5%).

α-(β′-*Hydroxyethyl*)-α-*phenylbutyrolactone* (III, R = OH).—A suspension of αα-bis-(β′-vinyloxyethyl)phenylacetonitrile (9·8 g.) in N-hydrochloric acid (75 c.c.) was heated on the water-bath with frequent shaking for one hour, and finally boiled for a few minutes. The oil was taken up in ether, which was washed with water and dried over anhydrous sodium sulphate. After removal of the solvent, the residue on distillation yielded (β′-*hydroxyethyl*)-α-*phenylbutyrolactone* as a slightly yellow, thick oil (5·1 g.), b. p. 172°/0·1 mm. (Found: C, 69·8; H, 7·2. $C_{12}H_{14}O_3$ requires C, 70·0; H, 6·8%).

α-(β′-*Bromoethyl*)-α-*phenylbutyrolactone* (III, R = Br).—αα-Bis-(β′-ethoxyethyl)phenylacetonitrile (10 g.) was heated for 2 hours in a sealed tube with an aqueous solution of hydrogen bromide (40 c.c.) saturated at 0°. The reaction product on being worked up as in the previous experiment yielded the *lactone* (III; R = Br) as a yellowish oil (7·3 g.), b. p. 140—142°/0·2 mm. (Found: C, 54·3; H, 5·1; Br, 30·2. $C_{12}H_{13}O_2Br$ requires C, 53·6; H, 4·8; Br, 29·8%).

α-(β′-*Chloroethyl*)-α-*phenylbutyrolactone* (III, R = Cl).—αα-Bis-(β′-hydroxyethyl)phenylacetonitrile (3·0 g.) was heated at 130° for 3 hours in a sealed tube with an aqueous solution of hydrogen chloride (25 c.c.) saturated at −20°. The product, worked up as above, gave the *lactone* (III; R = Cl) as a golden-yellow oil (Found: Cl, 15·5. $C_{12}H_{13}O_2Cl$ requires Cl, 15·6%).

α-(β′-*Piperidinoethyl*)-α-*phenylbutyrolactone* (III, R = $C_5H_{10}N$).—The bromo-lactone (III; R = Br) (4·0 g.) was dissolved in dry ether (5 c.c.), and piperidine (2·5 g.) in ether (3 c.c.) added slowly with stirring. After the mixture had stood at room temperature overnight, ether (10 c.c.) was added, and the mixture refluxed for 6 hours. The piperidine hydrobromide which separated was filtered off, and the ethereal solution extracted with dilute hydrochloric acid. α-(β′-*Piperidinoethyl*)-α-*phenylbutyrolactone*, precipitated from this solution by neutralisation with sodium hydroxide solution, distilled at 154°/0·1 mm. as a faintly yellow, viscous oil (2·5 g.) (Found: C, 74·7; H, 8·3; N, 5·2. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·4; N, 5·1%). Its *hydrochloride*, a white crystalline solid, after recrystallisation from alcohol melted at 216—217° (Found: C, 65·9; H, 7·8; N, 4·7. $C_{17}H_{24}O_2NCl$ requires C, 66·0; H, 7·8; N, 4·5%).

αα-Bis-(β′-bromoethyl)phenylacetic Acid (IV).—(*a*) 4-Phenylpentamethylene oxide-4-nitrile (5·0 g.) in an aqueous solution of hydrogen bromide (30 c.c.) saturated at −10° was heated in a sealed tube at 120—130° for 2 hours. After cooling, the excess hydrobromic acid was decanted from the solid, which was taken up in ether. After being washed with ice-water, the ethereal extract was concentrated, and benzene added. After further evaporation of solvents and cooling, the *dibromo-acid* (IV) was obtained as a crystalline, white solid (7·7 g.), m. p. 118° (Found: Br, 46·1. $C_{12}H_{14}O_2Br_2$ requires Br, 45·7%). It was prepared in an analogous manner from both αα-bis-(β′-hydroxyethyl)- and -(β′-ethoxyethyl)-phenylacetonitrile (I, R = H and R = Et).

(*b*) αα-Bis-(β′-vinyloxyethyl)phenylacetonitrile (10·0 g.) was suspended in water (30 c.c.), and hydrogen bromide passed through the mixture until the oil dissolved. The solution was then cooled to −10° and saturated with hydrogen bromide. It was heated in a sealed tube at 100—120° for 2 hours, and the product worked up as in the previous experiment. After purification with charcoal and recrystallisation from benzene–light petroleum (b. p. 60—80°), the acid was obtained as a grey-white powder, m. p. 115—118°. It was obtained in the same manner from αα-bis-(β′-methoxymethyloxyethyl)phenylacetonitrile.

Ethyl 4-Phenyl-1-methylpiperidine-4-carboxylate.—αα-Bis-(β′-bromoethyl)phenylacetic acid (8·0 g.) was dissolved in ethanol (50 c.c.), and the solution saturated with dry hydrogen chloride with external cooling. After standing for 5 days at room temperature, the mixture was poured on ice, and the ester extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate. After evaporation of the ether, a yellow oil (7 g.) remained, which was used without further purification for the condensation with methylamine. It was dissolved in alcohol (20 c.c.), and a 33% alcoholic solution of methylamine (15 c.c.) added to it. The mixture was then gradually heated during 2 hours to 110° in a sealed tube. After cooling, the solvents were evaporated under reduced pressure, and the residue dissolved in dilute hydrochloric acid. Non-basic material was removed by ether extraction. The aqueous part was then

made alkaline, and the liberated base extracted with ether. After being washed, and dried over anhydrous potassium carbonate, the ethereal extract was evaporated, and the residue distilled, giving ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (pethidine) as a mobile, colourless oil (b. p. 115°/0·2 mm.). Recrystallised from alcohol–ether, the hydrochloride melted at 187—189° alone and when mixed with an authentic specimen. It was also obtained in very small yield by treating crude ethyl $\alpha\alpha$-bis-(β'-chloroethyl)phenylacetate with methylamine in a similar manner to that described in the above experiment.

RESEARCH DEPARTMENT, ROCHE PRODUCTS LTD., WELWYN GARDEN CITY. [*Received, January 5th*, 1944.]

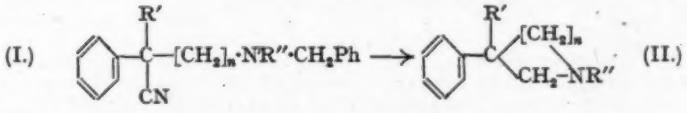
71. *Synthetic Analgesics. Part IV. Synthesis of 3-Substituted Piperidines and Pyrrolidines.**

By F. BERGEL, N. C. HINDLEY, A. L. MORRISON, and H. RINDERKNECHT.

New syntheses of 3-phenyl-pyrrolidine and -piperidine compounds are described. When benzylalkylaminoalkyl derivatives of phenylacetonitrile or ethyl phenylcyanoacetate were submitted to catalytic hydrogenation, reduction of the nitrile group occurred with simultaneous removal of the benzyl group and elimination of ammonia under ring closure. When *N*-dibenzylaminoalkyl derivatives were used, ring closure was followed by hydrogenolysis of the second benzyl group, yielding secondary cyclic bases. Catalytic hydrogenation of ω-cyanoalkyl derivatives of ethyl phenylcyanoacetate also gave secondary cyclic bases.

IN the three preceding papers certain aspects of the chemistry of 4-arylpiperidine compounds were discussed. We now present new syntheses of 3-phenyl-pyrrolidine and -piperidine compounds, some of which possess analgesic properties.

While attempting to prepare γ-methylamino-α-phenylbutyronitrile by selective hydrogenolysis of γ-benzylmethylamino-α-phenylbutyronitrile (I; R′ = H, R″ = CH_3; n = 2), we observed that 4-phenyl-1-methylpyrrolidine (II; R′ = H, R″ = CH_3; n = 2) was always formed. This is undoubtedly due to simultaneous reduction of the nitrile group, followed by elimination of ammonia to give a ring compound. This reaction



obviously afforded a general method of synthesising substituted pyrrolidines, and it was found that it could be extended to the preparation of substituted piperidines by hydrogenation of δ-benzylalkylamino-α-phenylvaleronitriles. Where R″ = CH_2Ph, it was found that the second benzyl radical was removed after ring closure, and secondary bases were formed (II; R″ = H).

Esters of 3-phenyl-1-methyl-pyrrolidine- and -piperidine-3-carboxylic acids were readily prepared by this method, starting from ethyl phenylcyanoacetate derivatives (I; R′ = CO_2Et, R″ = CH_3; n = 2 or 3). 3-Phenyl-1-methylpyrrolidine was also isolated from an attempt to prepare γ-methylamino-α-phenylbutyronitrile by hydrogenation of β-aldehydo-α-phenylpropionitrile in presence of methylamine.

3-Phenyl-1-methylpyrrolidine (II; R′ = H, R″ = CH_3; n = 2) was prepared by condensing phenylacetonitrile with β-chloroethylbenzylmethylamine in the presence of sodamide and hydrogenating the resulting *γ-benzylmethylamino-α-phenylbutyronitrile* (I; R′ = H, R″ = CH_3; n = 2). In a similar way *ethyl 3-phenyl-1-methylpyrrolidine-3-carboxylate* (II; R′ = CO_2Et, R″ = CH_3; n = 2) was obtained by catalytic hydrogenation of *ethyl α-cyano-γ-benzylmethylamino-α-phenylbutyrate* (I; R′ = CO_2Et, R″ = CH_3; n = 2).

For the syntheses of the corresponding piperidine derivatives *γ-chloropropylbenzylmethylamine* was prepared by the condensation of α-chloro-γ-bromopropane (from allyl chloride and hydrogen bromide) with benzylmethylamine (cf. Marxer, *Helv. Chim. Acta*, 1941, *E*, **24**, 214). Ethyl sodiophenylcyanoacetate when condensed with γ-chloropropylbenzylmethylamine gave *ethyl α-cyano-δ-benzylmethylamino-α-phenylvalerate* (I; R′ = CO_2Et, R″ = CH_3; n = 3), which on hydrogenation gave *ethyl 3-phenyl-1-methylpiperidine-3-carboxylate*. By starting from ethyl *o*-tolylcyanoacetate, the *o-tolyl* analogue was synthesised in the same manner.

As we also wished to prepare a piperidine derivative with a group other than phenyl in the 3-position, we condensed ethyl benzylcyanoacetate with γ-chloropropylbenzylmethylamine to give *ethyl α-cyano-δ-benzylmethylamino-α-benzylvalerate*, which on hydrogenation yielded *ethyl 3-benzyl-1-methylpiperidine-3-carboxylate*. *Ethyl 3-phenylpiperidine-3-carboxylate* was prepared most conveniently by condensation of ethyl sodiophenylcyanoacetate with α-chloro-γ-bromopropane in alcohol to give *ethyl δ-chloro-α-cyano-α-phenylvalerate*, which on heating with 2 mols. of dibenzylamine yielded *ethyl α-cyano-δ-dibenzylamino-α-phenylvalerate* (I; R′ = CO_2Et, R″ = CH_2Ph; n = 3). Catalytic hydrogenation gave the desired piperidine compound. Ethyl 3-phenylpiperidine-3-carboxylate was also synthesised by catalytic hydrogenation of *ethyl $\alpha\gamma$-dicyano-α-phenylbutyrate*, prepared by the condensation of ethyl phenylcyanoacetate with β-chloropropionitrile. Similarly, catalytic hydrogenation of *ethyl $\alpha\beta$-dicyano-α-phenylpropionate* (from ethyl phenylcyanoacetate and chloroacetonitrile) yielded *ethyl 3-phenylpyrrolidine-3-carboxylate*.

3-Phenyl-1-methylpyrrolidine was also prepared by catalytic hydrogenation of *β-aldehydo-α-phenyl-*

* Cf. B.P. 552,065 (1943); Pats. pend. Nos. 1310 and 3827 (1943).

propionitrile in presence of methylamine. The *acetal* of this aldehyde was formed by condensation of bromodiethylacetal with benzyl cyanide in presence of sodamide.

Studies of the resolution of the racemic compounds and of the properties of the optically active isomers will be published later. The pharmacology of the compounds will be reported in association with Professor A. D. Macdonald and Dr. G. Woolfe, University of Manchester (Department of Pharmacology).

Experimental.

γ-Chloropropylbenzylmethylamine.—Benzylmethylamine (37·8 g.) was added slowly with stirring to a solution of α-chloro-γ-bromopropane (24·5 g.) in ether (25 c.c.) at room temperature. The mixture was warmed at 30° for 90 minutes, the water-bath then heated to 40—45°, and stirring continued for 7 hours. The crystalline benzylmethylamine hydrobromide was filtered off, and the ethereal solution extracted with dilute hydrochloric acid. The extract was made alkaline, and the oil which separated taken up in ether, and dried over anhydrous sodium sulphate. *γ-Chloropropylbenzylmethylamine* distilled at 137—138°/16 mm. as a colourless oil (19·4 g.) (Found: N, 7·2; Cl, 18·3. $C_{11}H_{16}NCl$ requires N, 7·1; Cl, 18·0%). On prolonged standing it underwent autocondensation.

β-Cyano-β-phenylpropaldehyde Diethylacetal.—Phenylacetonitrile (13·0 g.) was added slowly with stirring to powdered sodamide (4·3 g.) suspended in dry ether (50 c.c.), the mixture refluxed for 10 minutes, then cooled to 0°; bromoacetal (21·7 g.) was then added slowly (2 hours), and stirring continued at room temperature overnight. The reaction mixture was poured on ice, the ethereal layer separated, washed with water, dried over anhydrous sodium sulphate, and evaporated. The residue was distilled, and the *acetal* obtained as a colourless oil (10 g.), b. p. 120—121°/0·2 mm. (Found: N, 5·8. $C_{14}H_{19}O_2N$ requires N, 6·0%).

β-Cyano-β-phenylpropaldehyde.—The acetal (5 g.) was shaken with 15% hydrochloric acid (20 c.c.) for 24 hours in nitrogen. The mixture was then extracted with ether, and the extract washed with dilute potassium carbonate solution, dried over anhydrous sodium sulphate, and evaporated. The residue on distillation gave the *aldehyde* (2·7 g.) as a colourless oil, b. p. 109—111°/0·1 mm. (Found: N, 8·6. $C_{10}H_9ON$ requires N, 8·8%).

γ-Benzylmethylamino-α-phenylbutyronitrile (I; R′ = H, R″ = CH_3; *n* = 2).—Phenylacetonitrile (48 g.) was added slowly with stirring to powdered sodamide (16·2 g.) suspended in dry ether (260 c.c.), and the mixture refluxed for 20 minutes and then cooled to 15°; β-chloroethylbenzylmethylamine (69 g.) was now added slowly (30 minutes), and stirring continued overnight. The mixture was poured into water, the ethereal layer extracted with dilute hydrochloric acid, the extract made alkaline, and the oil which separated taken up in ether. After being washed, and dried over anhydrous sodium sulphate, the ether was evaporated. The residue was distilled, giving *γ-benzylmethylamino-α-phenylbutyronitrile* (74 g.) as a yellow oil, b. p. 158°/0·1 mm. (Found: N, 10·7. $C_{18}H_{20}N_2$ requires N, 10·6%). Its *reineckate* melted at 104—107° (Found: N, 19·0. $C_{22}H_{36}N_8S_4Cr$ requires N, 19·2%).

3-Phenyl-1-methylpyrrolidine (I; R′ = H; R″ = CH_3).—(A) β-Cyano-β-phenylpropaldehyde (2 g.) was reduced catalytically with palladium–charcoal (1 g. of charcoal + 5 c.c. of 5% aqueous palladium chloride) in a mixture of alcohol and a 33% aqueous solution of methylamine (5 c.c.). When the hydrogen absorption had ceased, the mixture was filtered and the solvents evaporated. The residue was extracted with dilute hydrochloric acid, the extract made alkaline, the precipitated base taken up in ether, the ethereal solution dried (potassium carbonate), and the ether evaporated; the residue was distilled to give a small amount of 3-phenyl-1-methylpyrrolidine. Recrystallised from water, its *picrate* melted at 155—158° (Found: C, 52·5; H, 5·3; N, 14·5. $C_{17}H_{18}O_7N_4$ requires C, 52·4; H, 4·6; N, 14·4%).

(B) γ-Benzylmethylamino-α-phenylbutyronitrile (9·2 g.) was reduced catalytically in methanol solution, the catalyst being 2 g. of charcoal and 12 c.c. of 5% aqueous palladium chloride solution containing 6% hydrogen chloride. When hydrogen absorption had ceased, the mixture was worked up in the usual manner, giving 3-phenyl-1-methylpyrrolidine as a colourless oil, b. p. 105—110°/11 mm. Its picrate melted at 155—158° alone and when mixed with that described in (A).

Ethyl α-Cyano-γ-benzylmethylamino-α-phenylbutyrate (I; R′ = CO_2Et, R″ = CH_3; *n* = 2).—(A) Sodium wire (0·43 g.) was covered with dry ether (50 c.c.), and ethyl phenylcyanoacetate (3·5 g.) added slowly with stirring. When the sodium had dissolved, a solution of β-chloroethylbenzylmethylamine (3·5 g.) in dry toluene (50 c.c.) was added, the ether distilled off, and the toluene solution heated on the water-bath for 16 hours. After cooling, the reaction mixture was poured into water, and the toluene layer separated. After removal of the solvent, the product was distilled, giving *ethyl α-cyano-γ-benzylmethylamino-α-phenylbutyrate* as a yellow oil (5·4 g.), b. p. 176—178°/0·2 mm. (Found: C, 75·6; H, 7·2; N, 8·1. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1; N, 8·3%).

(B) Ethylene dibromide (7·6 g.) was added to a solution of ethyl sodiophenylcyanoacetate (7·6 g. ester, 0·5 g. sodium) in absolute alcohol (12 c.c.), and the mixture heated in a sealed tube at 115° for 3 hours. The sodium bromide was filtered off, and the alcohol evaporated. The residue was taken up in ether, the solution washed with water, and dried by distilling with benzene. The remaining oil (9·2 g.) was heated in alcoholic benzylmethylamine solution (6·1 g. in 10 c.c.) in a sealed tube at 100° for 2 hours, the product filtered, and the solvent evaporated. The residual oil was taken up in ether, and the ethereal solution extracted with dilute hydrochloric acid, the acid extract made alkaline, and the oil which separated taken up in ether. After washing, drying, and evaporation of the extract, the residue was distilled. The oil boiled at 174—180°/0·2 mm. Its identity was proved by hydrogenation, which gave (II; R′ = CO_2Et, R″ = CH_3; *n* = 2).

Ethyl 3-Phenyl-1-methylpyrrolidine-3-carboxylate (II; R′ = CO_2Et, R″ = CH_3; *n* = 2).—A mixture of aqueous 5% palladium chloride solution (10 c.c.) containing 6% of hydrogen chloride, charcoal (1 g.), and alcohol (50 c.c.) was shaken in a hydrogen atmosphere until absorption of hydrogen ceased. Ethyl α-cyano-γ-benzylmethylamino-α-phenylbutyrate (2·4 g.) was then added, and the hydrogenation continued. When the absorption of hydrogen had ceased, the reaction mixture was filtered and worked up as described above. The *ester* distilled at 114°/0·4 mm. as a colourless oil (Found: C, 72·2; H, 8·4. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2%). Its *picrate* melted at 115—118° after recrystallisation from alcohol (Found: C, 51·7; H, 4·7; N, 12·3. $C_{20}H_{22}O_9N_4$ requires C, 51·9; H, 4·7; N, 12·1%).

Ethyl α-Cyano-δ-benzylmethylamino-α-phenylvalerate (I; R′ = CO_2Et, R″ = CH_3; *n* = 3).—Ethyl phenylcyanoacetate (18·9 g.) was dissolved in dry toluene (150 c.c.), and powdered sodamide (4·0 g.) added in several portions with mechanical stirring. The mixture was gradually heated to boiling, refluxed for 30 minutes, and cooled to room temperature; γ-chloropropylbenzylmethylamine (21 g.) was added, and the mixture slowly heated to boiling and refluxed for 2 hours. The product was treated with water, the toluene layer separated, washed with water, and evaporated under reduced pressure. The residue was distilled in a high vacuum. The *ester* distilled at 180°/0·2 mm. as a thick yellow oil (26·8 g.) (Found: C, 75·9; H, 7·7; N, 8·3. $C_{22}H_{26}O_2N_2$ requires C, 75·5; H, 7·5; N, 8·0%).

Ethyl 3-Phenyl-1-methylpiperidine-3-carboxylate (II; R′ = CO_2Et, R″ = CH_3; *n* = 3).—A mixture of aqueous 5% palladium chloride solution, containing 6% of hydrogen chloride (20 c.c.), charcoal (6 g.), and alcohol (200 c.c.) was shaken in a hydrogen atmosphere until hydrogen absorption ceased. Ethyl α-cyano-δ-benzylmethylamino-α-phenylvalerate (12·8 g.) was then added, and shaking resumed. The absorption of hydrogen was very rapid. When it had slackened, an additional portion of palladium chloride solution (5 c.c.) was added, and hydrogenation carried to completion. The

product was worked up as described in previous experiments. The *ester* (5·6 g.) distilled as a colourless oil at 104°/0·2 mm. (Found : C, 72·9; H, 8·6; N, 5·7. $C_{15}H_{21}O_2N$ requires C, 72·8; H, 8·5; N, 5·7%). Its *hydrochloride*, a white, hygroscopic crystalline solid melted at 177—180° after recrystallisation from alcohol–ether (Found : C, 62·9; H, 7·9; N, 5·0; Cl, 12·4. $C_{15}H_{22}O_2NCl$ requires C, 63·6; H, 7·8; N, 5·0; Cl, 12·4%). The *hydriodide* after recrystallisation from alcohol had m. p. 207° (Found : C, 48·3; H, 6·0; N, 3·7; I, 34·3. $C_{15}H_{22}O_2NI$ requires C, 48·0; H, 5·9; N, 3·7; I, 33·9%).

3-Phenyl-1-methylpiperidine-3-carboxylic Acid.—The above ester (2·5 g.) was refluxed with 10% alcoholic potash solution (50 c.c.) for 2 hours, the solvent evaporated, and the residue made acid to Congo-red with dilute hydrochloric acid. The acid solution was evaporated to dryness under reduced pressure, and the salts were dried over phosphoric oxide. After extraction with absolute alcohol, filtration, and evaporation of the alcohol, the residue was sublimed in a high vacuum (oil bath : 200°/0·1 mm.). The hydrochloride of the acid was obtained in white needles, m. p. 265°. The *picrate* had m. p. 196—199° after recrystallisation from alcohol (Found : C, 50·3; H, 4·5; N, 12·5. $C_{19}H_{20}O_9N_4$ requires C, 50·9; H, 4·5; N, 12·5%).

Methyl ester. Thionyl chloride (50 c.c.) was added to the crude mixture of potassium chloride and acid hydrochloride obtained as described above. After refluxing for 15 minutes, the excess of thionyl chloride was distilled off under reduced pressure. Dry methanol (15 c.c.) was added, the mixture refluxed for 15 minutes, the excess of methanol distilled off, and the residue taken up in ice-cold dilute hydrochloric acid and extracted with ether. The aqueous layer was made alkaline and extracted with ether; the extract was washed with water, dried (sodium sulphate), and evaporated; distillation of the residue gave the methyl ester (1·4 g.) as a colourless oil, b. p. 110°/0·4 mm. Recrystallised from methanol–ether, its *hydrochloride* melted at 177—179° (Found : C, 61·2; H, 7·4; N, 5·6; Cl, 12·6. $C_{14}H_{20}O_2NCl$ requires C, 62·4; H, 7·5; N, 5·2; Cl, 13·0%).

The *n*-propyl ester, similarly prepared, was a colourless oil, b. p. 110°/0·2 mm.; *hydrochloride*, m. p. 174—175° (Found : C, 63·1; H, 8·2; N, 4·8; Cl, 12·5. $C_{16}H_{24}O_2NCl$ requires C, 64·6; H, 8·1; N, 4·7; Cl, 11·8%). The *iso*propyl ester had b. p. 110°/0·2 mm., and gave a *hydrochloride*, m. p. 191—193° (Found : C, 64·6; H, 8·4; N, 4·6; Cl, 11·5%).

The *diethylamide*, prepared by treatment of the acid chloride with an excess of diethylamine at 0°, distilled at 125—128°/0·1 mm. as a thick yellow oil; yield 74% (Found : C, 74·7; H, 9·5; N, 10·6. $C_{17}H_{26}O_2N_2$ requires C, 74·5; H, 9·5; N, 10·2%).

Ethyl o-Tolylcyanoacetate.—A solution of *o*-tolylacetonitrile (21·5 g.) in dry ether (40 c.c.) was added slowly to powdered sodamide (7·2 g.) suspended in dry ether (70 c.c.) with mechanical stirring, and the mixture refluxed for 15 minutes. Ethyl carbonate (25 g.) was then added slowly with external cooling, and the reaction completed by refluxing for 90 minutes. The mixture was then poured into ice water, the ethereal layer separated, washed with water, dried over anhydrous sodium sulphate, and evaporated. The residue on distillation gave *ethyl o-tolylcyanoacetate* (19·8 g.) as a faintly yellow oil, b. p. 110—114°/0·1 mm. (Found : N, 7·1. $C_{12}H_{13}O_2N$ requires N, 6·9%).

Ethyl α-Cyano-δ-benzylmethylamino-α-o-tolylvalerate.—Powdered sodamide (1·2 g.) was added in several portions to a solution of the above ester (6·1 g.) in dry toluene (50 c.c.) with mechanical stirring, and the mixture finally refluxed for 15 minutes. γ-Chloropropylbenzylmethylamine (6·0 g.) was then added gradually with external cooling, and the reaction completed by 3 hours' refluxing. The mixture was then treated with dilute hydrochloric acid, and the insoluble oily hydrochloride separated, treated with alkali, and extracted with ether. The ethereal extract was washed with water, dried (potassium carbonate), and evaporated. The *nitrile* (7·1 g.) distilled at 199—200°/0·2 mm. as a yellow, viscous oil (Found : C, 75·1; H, 7·9; N, 7·7. $C_{23}H_{28}O_2N_2$ requires C, 75·8; H, 7·8; N, 7·7%).

Ethyl 3-(o-Tolyl)-1-methylpiperidine-3-carboxylate.—A mixture of charcoal (6 g.), 5% aqueous palladium chloride solution containing 6% of hydrogen chloride (10 c.c.), and alcohol (250 c.c.) was shaken in a hydrogen atmosphere until hydrogen absorption ceased. The foregoing ester (6·6 g.) and an additional portion of palladium chloride solution (5 c.c.) were then added, and hydrogenation continued until no more hydrogen was absorbed. The product was worked up as described in previous examples. The *ester*, a colourless oil (3·2 g.), distilled at 126—128°/0·2 mm. (Found : N, 5·9. $C_{16}H_{23}O_2N$ requires N, 5·4%). Recrystallised from alcohol–ether, the *hydrochloride* had m. p. 200—201° (Found : C, 64·8; H, 8·2; Cl, 11·9. $C_{16}H_{24}O_2NCl$ requires C, 64·7; H, 8·1; Cl, 11·8%). The *hydriodide*, recrystallised from alcohol, had m. p. 178—180° (Found : N, 3·5. $C_{16}H_{24}O_2NI$ requires N, 3·6%).

Ethyl α-Cyano-δ-benzylmethylamino-α-benzylvalerate.—Ethyl benzylcyanoacetate (10 g.) and γ-chloropropylbenzylmethylamine (11 g.) were dissolved in toluene (100 c.c.), and powdered sodamide (2·4 g.) added gradually with vigorous stirring. The mixture was then refluxed for 7 hours. On being worked up in the usual manner, the basic *ester* was obtained as a viscous oil, b. p. 225—235°/0·4 mm. (Found : C, 76·3; H, 8·0; N, 7·5. $C_{23}H_{28}O_2N_2$ requires C, 75·8; H, 7·7; N, 7·7%).

Ethyl 3-Benzyl-1-methylpiperidine-3-carboxylate.—The above ester (5 g.) was hydrogenated in alcohol with a catalyst prepared from charcoal (2 g.) and 5% palladium chloride (10 c.c.), with the addition of a further 2 c.c. of the latter after hydrogenation had started. When hydrogen uptake had ceased, the catalyst was filtered off, the filtrate concentrated, water added, and the aqueous solution made alkaline with sodium hydroxide solution. The liberated base was taken up in ether, the solution dried, concentrated, and the residue distilled, giving *ethyl 3-benzyl-1-methylpiperidine-3-carboxylate* (2·1 g.), b. p. 125—135°/0·3 mm. (Found : C, 74·3; H, 9·2; N, 5·6. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%).

Ethyl δ-Chloro-α-cyano-α-phenylvalerate.—To a solution of sodium (0·92 g.) in absolute alcohol (40 c.c.) and ethyl phenylcyanoacetate (8·0 g.), α-chloro-γ-bromopropane (12·6 g.; 2 mols.) was added, and the mixture heated on a water-bath with mechanical stirring for 7 hours. The product was filtered, the alcohol evaporated, and the residual oil taken up in ether. The extract was washed with water, dried over anhydrous sodium sulphate, and evaporated. The *ester* distilled at 128—129°/0·1 mm. as a colourless oil (9·6 g.) (Found : N, 5·0. $C_{14}H_{16}O_2NCl$ requires N, 5·3%).

Ethyl α-Cyano-δ-dibenzylamino-α-phenylvalerate (I; R′ = CO_2Et, R″ = CH_2Ph; *n* = 3).—A solution of ethyl δ-chloro-α-cyano-α-phenylvalerate (43·5 g.), dibenzylamine (65·25 g.), and sodium iodide (26·95 g.) in dry acetone (200 c.c.) was refluxed for 21 hours. After cooling, the reaction mixture was filtered, the acetone evaporated, and the residue taken up in ether. After being washed with dilute sodium hydroxide solution and water, and dried over potassium carbonate, the extract was evaporated. The *ester* distilled as a yellow, viscous oil (64·5 g.) at 215—217°/0·1 mm. (Found : C, 79·8; H, 7·2; N, 7·0. $C_{35}H_{36}O_2N_2$ requires C, 78·8; H, 7·0; N, 6·6%).

Ethyl αγ-Dicyano-α-phenylbutyrate.—To a solution of ethyl phenylcyanoacetate (15·0 g.) in dry toluene (75 c.c.), powdered sodamide (3·1 g.) was added with mechanical stirring, and the mixture refluxed for 15 minutes. A solution of β-chloropropionitrile (7·0 g.) in dry toluene (5 c.c.) was then added, and refluxing continued for 2 hours. The product was cooled, poured into water, and the toluene layer separated, washed with water, and evaporated under reduced pressure. The *ester* distilled as a colourless oil (12·2 g.) at 145°/0·1 mm. (Found : C, 69·5; H, 5·8; N, 11·7. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

Ethyl αβ-Dicyano-α-phenylpropionate.—To a solution of ethyl phenylcyanoacetate (11 g.) in dry toluene (50 c.c.), powdered sodamide (2·1 g.) was added, and the sodio-derivative prepared as in the above experiment. Chloroacetonitrile (4·0 g.) was then added, and after refluxing for 2 hours the reaction mixture was worked up as above. The *ester* distilled as a colourless oil (8·1 g.) at 141—142°/0·1 mm. (Found : C, 68·9; H, 5·6; N, 11·8. $C_{12}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

Ethyl 3-*Phenylpiperidine*-3-*carboxylate* (II; R′ = CO_2Et, R″ = H; *n* = 3).—(A) A mixture of charcoal (12 g.), 10% aqueous palladium chloride solution (5 c.c.) containing 6% of hydrogen chloride, alcohol (200 c.c.), and water (50 c.c.) was shaken in a hydrogen atmosphere until no more hydrogen was taken up. Ethyl α-cyano-δ-dibenzylamino-α-phenylvalerate (12·9 g.) and an alcoholic solution of hydrogen chloride (4 c.c. of 5·67N) were then added, and the hydrogenation continued, the temperature being kept at approx. 40°. When the absorption of hydrogen had slackened, a further 3 c.c. of palladium chloride solution were added, and the hydrogenation carried to completion. After filtration, the product was worked up as previously described. The *ester* (5·3 g.) distilled at 115—117°/0·1 mm. as a colourless oil (Found: C, 70·6, 70·7; H, 8·4, 8·1; N, 6·2. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·1%). It formed a solid *nitroso*-derivative, m. p. 88—89° after recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 63·9; H, 6·9; N, 10·6. $C_{14}H_{18}O_3N_2$ requires C, 64·1; H, 6·9; N, 10·7%).

(B) Hydrogenation of ethyl αγ-dicyanobutyrate (2·2 g.) was effected as before by means of a mixture of charcoal (3 g.), 10% aqueous palladium chloride solution (10 c.c.) containing 6% of hydrogen chloride, and alcohol (100 c.c.), a further 0·2 g. of catalyst being used later. The product was worked up as in the previous experiment. A colourless oil (0·8 g.) was obtained, b. p. 115—117°/0·1 mm., which gave a nitroso-derivative identical with that obtained in the preceding experiment.

Ethyl 3-*Phenylpyrrolidine*-3-*carboxylate* (II; R′ = CO_2Et, R″ = H; *n* = 2).—Ethyl αβ-dicyano-α-phenylpropionate (2·3 g.) was hydrogenated, palladised charcoal being used as catalyst [prepared from charcoal (4 g.), 5% aqueous palladium chloride solution (10 c.c.), and alcohol (75 c.c.)]. Hydrogenation proceeded very slowly and several portions of palladium chloride solution (total 17 c.c.) and platinum oxide (0·2 g.) had to be added to complete it. The product was worked up as above. The *ester* (0·6 g.) distilled at 97°/0·1 mm. as a colourless oil (Found: C, 71·8; H, 8·0; N, 6·6. $C_{13}H_{17}O_2N$ requires C, 71·3; H, 7·8; N, 6·4%).

We wish to express our thanks to Misses E. M. Cronin, M. D. Gillman, and M. L. Junion, and to Messrs. H. G. Pallett and A. H. Winn for their valuable assistance in the experimental work in this series of papers.

Research Department, Roche Products Ltd., Welwyn Garden City. [*Received, January 5th*, 1944.]

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72. *Derivatives of Chondrosamine.*

By Maurice Stacey.

A convenient method is described for preparing chondrosamine hydrochloride. By application of processes developed for the glucosamine series, a number of acetylated and methylated derivatives of chondrosamine have been synthesised.

Attention has recently been directed to the widespread occurrence of biologically important polysaccharides containing amino-sugars (Stacey, *J. Soc. Chem. Ind.*, 1942, **61**, 110). Two naturally occurring aminohexoses have so far been recognised, *viz.*, glucosamine and chondrosamine.

The formulation of glucosamine as 2-aminoglucose has been established by Haworth, Lake, and Peat (J., 1939, 271) and independently by Cox and Jeffrey (*Nature*, 1939, **143**, 984), but the configuration of the amino-group in chondrosamine has not yet been established. This sugar has been less accessible than glucosamine; it occurs in combination with acetic acid, sulphuric acid, and glucuronic acid residues in the chondroitin sulphate of cartilaginous tissues. When this investigation was begun, the only known derivatives of chondrosamine were the penta-acetates and certain Schiff's bases, so it was decided to prepare characteristic derivatives of value in the elucidation of polysaccharide structure, but in the meantime work along identical lines has been published by Levene (*J. Biol. Chem.*, 1941, **137**, 29). Adopting methods worked out by Cutler, Haworth, and Peat (J., 1937, 1979), he prepared fully methylated *N*-acetylchondrosamine and oxidised this with mercuric oxide to the corresponding chondrosaminic acid, which was then degraded by means of chloramine-T to 2 : 3 : 5-trimethyl lyxose. On this evidence, a pyranose structure was ascribed to *N*-acetyl trimethyl methylchondrosaminide. Although Levene failed to obtain crystalline derivatives in the final oxidation sequence, there is no reason to doubt that his conclusions are correct, since the properties of the α- and the β-form of the fully methylated *N*-acetyl chondrosamine described below are those of pyranosides and bear a close analogy to the corresponding glucosamine derivatives which have been shown to have the pyranoside structure. Levene failed to separate and characterise the α- and the β-form of his fully methylated *N*-acetyl chondrosamine although it is evident that he had prepared a mixture of the two forms.

The source of the chondrosamine used in the present study was chondroitin sulphate prepared from the cartilage of bovine nasal septa. A convenient method for preparing the hydrochloride of the amino-sugar in good yield was devised. In collaboration with Dr. G. A. Jeffrey, in this department, it was discovered that the *X*-ray powder photograph of chondrosamine hydrochloride was quite distinct from that of glucosamine hydrochloride, and we have applied this property as a means of identifying and distinguishing small amounts of the two amino-sugars in biological material. When the hydrochloride is obtainable in crystalline form the method has distinct advantages over the identification methods described by Chargaff and Bovarnick (*J. Biol. Chem.*, 1937, **118**, 421) and by Jolles and Morgan (*Biochem. J.*, 1940, **34**, 1183).

Levene ("Hexosamine and Mucoproteins," 1925) has presented evidence that chondrosamine is either 2-amino-galactose or 2-amino-talose. We have confirmed that treatment of its hydrochloride with phenylhydrazine affords galactosazone, but the present investigation has provided no evidence as to the orientation of the amino-group on the second carbon atom in chondrosamine.

When the acetylation of chondrosamine was carried out by acetic anhydride and pyridine, the crystalline product obtained was the α-*penta-acetate* (yield 60%), m. p. 178°, $[\alpha]_D$ +102° in chloroform, the residue being an

amorphous mixture of the α- and the β-form of the penta-acetate. When, however, zinc chloride was used as catalyst in the acetylation, the sole crystalline product was the β-*penta-acetate* (yield 30%), m. p. 235°, $[\alpha]_D$ +7° in chloroform.

N-Acetyl chondrosamine was conveniently prepared by the action of silver acetate in dry methyl alcohol on chondrosamine hydrochloride. It crystallised as a *monohydrate* (m. p. 120—122°), and from the direction of its mutarotation in water ($[\alpha]_D$ +115° ⟶ +80°) it was evidently the α-form. Treatment of penta-acetyl chondrosamine with methyl-alcoholic hydrogen chloride (cf. Moggridge and Neuberger, J., 1938, 745) gave in quantitative yield N-*acetyl α-methylchondrosaminide*, m. p. 217—218°, $[\alpha]_D$ +170° in chloroform. From this compound, *N*-acetyl trimethyl α-methylchondrosaminide was obtained in good yield on methylation with silver oxide and methyl iodide. An alternative route to the same substance was found in the methylation, in alkaline solution, of α-penta-acetyl chondrosamine, Cutler, Haworth, and Peat's method (*loc. cit.*) for glucosamine being used. The *N*-acetyl group in the chondrosamine series exhibits a stability in the presence of alkali comparable with that of the *N*-acetyl group in corresponding glucosamine derivatives under the same conditions.

When β-penta-acetyl chondrosamine was methylated with methyl sulphate and sodium hydroxide, the crystalline product (45% yield) was *N*-acetyl trimethyl β-methylchondrosaminide. Hence, it was expected that methylation of a mixture of α- and β-penta-acetyl chondrosamine would yield the α- and the β-form of *N*-acetyl trimethyl methylchondrosaminide. This was found to be the case, and the two isomers were separated by fractional crystallisation from ethyl acetate in which the β-form was the less soluble.

The relationship between the two isomers was established when it was found that by boiling the β-form with 1% methyl-alcoholic hydrogen chloride it was quantitatively transformed into the α-form. This conversion exactly parallels that obtained by Cutler, Haworth, and Peat (*loc. cit.*) with the corresponding glucosamine derivative.

On hydrolysis with N-hydrochloric acid, *N*-acetyl trimethyl α-methylchondrosaminide gave trimethyl chondrosamine hydrochloride, m. p. 178°, $[\alpha]_D$ +114° in water, having properties essentially the same as those described by Levene (*loc. cit.*).

Attempts to make acetobromochondrosamine gave products in which the bromine was unexpectedly labile and which readily yielded *tetra-acetyl chondrosamine monohydrate*.

Experimental.

Chondrosamine Hydrochloride.—The barium salt of chondroitin sulphate (11 g.) was dissolved in cold concentrated hydrochloric acid (250 c.c.), and the solution boiled under reflux (12 hours) until it no longer gave a Molisch test for carbohydrate or a naphtharesorcin test for uronic acid. The dark solution was boiled with charcoal (2 g.) for a further 15 minutes, filtered, and evaporated to a syrup under diminished pressure. Crystalline barium chloride which separated was stirred with methyl alcohol and filtered off. The methyl-alcoholic solution was evaporated to a syrup from which a further small quantity of barium chloride was separated by stirring it with methyl alcohol containing 10% of acetone. On concentration of the solution the residue set to a solid mass. It was kept for 24 hours and then stirred with methyl alcohol–acetone and filtered off (yield 4·3 g.). A further quantity was isolated from the concentrated mother-liquors. The product, recrystallised from aqueous methyl alcohol, had $[\alpha]_D^{20°}$ +105° ⟶ +96°, equilibrium value in water after 24 hours (Found: N, 6·4; Cl, 14·5. Calc. for $C_6H_{14}O_5NCl$: N, 6·4; Cl, 14·8%). The crystallographic and *X*-ray analysis will be described elsewhere. When heated at 80° in aqueous solution with an excess of phenylhydrazine acetate, the compound afforded galactosazone in 40% yield.

α-*Penta-acetyl Chondrosamine.*—Chondrosamine hydrochloride (4 g.) was suspended in dry pyridine (100 c.c.) and shaken with acetic anhydride (100 c.c.) for 60 hours. The pale yellow solution was decanted from a small amount of undissolved material (100 mg.) and evaporated to a syrup in a vacuum. The syrup was dissolved in chloroform (300 c.c.) and the solution washed 3 times with distilled water. The chloroform solution was dried over calcium chloride and concentrated to a syrup, which rapidly crystallised. Recrystallised from alcohol–light petroleum, the crystals (2·5 g.) had m. p. 178°; $[\alpha]_D^{20°}$ +102° in chloroform (*c*, 1·6) (Found: C, 49·5; H, 6·1; N, 3·9; OAc, 55·1. $C_{16}H_{23}O_{10}N$ requires C, 49·3; H, 6·0; N, 3·6; OAc, 55·3%). The aqueous washings gave on evaporation a syrupy mixture of the α- and the β-form of the penta-acetate, which failed to crystallise.

β-*Penta-acetyl Chondrosamine.*—Chondrosamine hydrochloride (6 g.) was suspended in acetic anhydride (75 c.c.) and shaken with powdered anhydrous zinc chloride (2 g.) for 24 hours. The solution was poured into ice-water (4 vols.), cautiously neutralised with sodium carbonate, made faintly alkaline with sodium hydroxide, and then extracted six times with chloroform (75 c.c. portions). The combined extracts were dried over anhydrous magnesium sulphate and then evaporated in a vacuum. When crystallisation commenced, the solution was diluted with ethyl alcohol and kept overnight at 0°. Crystallised from chloroform–ethyl alcohol, the crystals (3·2 g.) had m. p. 235°; $[\alpha]_D^{20°}$ +7° (*c*, 0·6) in chloroform (Found: C, 48·9; H, 6·0; N, 3·5; OAc, 54·8%). A further crop of crystals (0·4 g.) was separated from the mother-liquors, the main constituent of which was a syrupy mixture of the α- and the β-form of penta-acetyl chondrosamine. It was converted (see p. 274) into tetra-acetyl chondrosamine.

N-Acetyl Chondrosamine.—Chondrosamine hydrochloride (2 g.) and silver acetate (1 g.) were suspended in dry methyl alcohol containing a few drops of acetic anhydride, and then shaken vigorously for 3 hours. The solution was heated for a few minutes at 50°, diluted with a little ether, filtered, and concentrated to a syrup which crystallised on being kept. Recrystallised from ethyl acetate–methyl alcohol, it had m. p. 120—122°; $[\alpha]_D^{21°}$ +115° ⟶ 80° after 50 hours (equilibrium value in water) (Found: C, 39·8; H, 7·2; N, 5·9. $C_8H_{15}O_6N,H_2O$ requires C, 40·1; H, 7·1; N, 5·9%). A Van Slyke estimation showed the absence of a primary amino-group.

N-Acetyl α-Methylchondrosaminide.—α-Penta-acetyl chondrosamine (1·5 g.) was dissolved in 2% methyl-alcoholic hydrogen chloride (150 c.c.) and boiled for 90 minutes ($[\alpha]_D^{21°}$ +107° ⟶ +83°). The solution was neutralised with silver carbonate, filtered, and evaporated in a vacuum, leaving a crystalline mass. This was dissolved in a small amount of alcohol, and ether added to precipitate a little colloidal silver salt which was filtered off. After removal of the solvent, the product (0·9 g.) was recrystallised several times from alcohol–light petroleum. It had m. p. 217—218°, $[\alpha]_D^{21°}$ +170° in chloroform, and did not reduce Fehling's solution (Found: C, 45·6; H, 7·2; N, 6·3; OMe, 13·7. $C_9H_{17}O_6N$ requires C, 45·9; H, 7·3; N, 6·0; OMe, 13·2%). The product tended to separate in a gelatinous form. It was also prepared in quantitative yield from an amorphous mixture of α- and β-penta-acetates.

N-Acetyl Trimethyl α-Methylchondrosaminide (This substance and its β-isomer were first isolated in 1938 from methylated chondrosine in these laboratories in collaboration with Dr. T. White).—*From N-acetyl α-methylchondrosaminide.* The glucoside (0·5 g.) was dissolved in methyl iodide (20 c.c.) containing dry methyl alcohol (1 c.c.), and the solution boiled with silver oxide (2 g.) for 4 hours. Chloroform (50 c.c.) was added, and the filtered solution concentrated to a semi-solid mass, which was again methylated by the same reagents. The product obtained on evaporation of the solvent was crystallised from ethyl acetate–light petroleum (yield 0·6 g.); m. p. 185°, $[\alpha]_D^{20°}$ +121° in chloroform (*c*, 1·4) (Found: C, 51·8; H, 8·3; N, 5·0; OMe, 43·8. Calc. for $C_{12}H_{23}O_6N$: C, 52·0; H, 8·3; N, 5·1; OMe, 44·8%). The substance readily sublimed at 187°, forming long, feathery needles. A Van Slyke estimation showed the absence of a primary amino-group.

From α-penta-acetyl chondrosamine. The crystalline α-penta-acetate (p. 273) was methylated by sodium hydroxide and methyl sulphate in the presence of carbon tetrachloride by essentially the same method as that described by Cutler, Haworth, and Peat (*loc. cit.*). The product had m. p., and mixed m. p. with the methylated derivative described above, 185°; $[\alpha]_D^{20°}$ +120° in chloroform (*c*, 1·0) (Found: C, 51·9; H, 8·3; N, 5·1; OMe, 44·3%). It was soluble in chloroform, ether, alcohol, and acetone, and insoluble in light petroleum.

N-Acetyl Trimethyl β-Methylchondrosaminide.—β-Penta-acetyl chondrosamine (3 g.) was methylated with potassium hydroxide and methyl sulphate at 45—50° in the presence of acetone and carbon tetrachloride. The solution was stirred for 5 hours, neutralised, and extracted with chloroform, removal of which left a crystalline residue (0·55 g.), m. p. 212—215°. The aqueous mother-liquor was evaporated to a solid, which was extracted with ethyl alcohol. This was also evaporated, and the syrupy product extracted with chloroform. On evaporation of the solvent there remained a syrup which was boiled for 10 minutes in methyl alcohol containing acetic anhydride, and the solvents were then distilled off. The residue was methylated with silver oxide and methyl iodide and there was obtained a product (1·25 g.), m. p. 220°, which was combined with the first crop (0·55 g.) and recrystallised (twice) from ethyl acetate–light petroleum; m. p. 232°, $[\alpha]_D^{20°}$ +7° in chloroform (*c*, 0·95) (Found: C, 51·8; H, 8·3; N, 5·3; OMe, 44·1%). A Van Slyke estimation showed the absence of a primary amino-group. The product can be purified by sublimation at 235°.

N-Acetyl Trimethyl αβ-Chondrosaminide.—When an amorphous mixture of α- and β-penta-acetyl chondrosamine (2 g.) was methylated with potassium hydroxide and methyl sulphate by the method described above, there was obtained a crystalline mass (1·2 g.), m. p. 160—170°, which when fractionally crystallised from dry ethyl acetate gave *N*-acetyl trimethyl α-methylchondrosaminide (1·5 g.), m. p. 185°, $[\alpha]_D^{21°}$ +121°, and its β-isomer (0·35 g.), m. p. 233°, $[\alpha]_D^{20°}$ +14° in chloroform (*c*, 1·1). These two compounds could be partly separated by fractional sublimation in a high vacuum.

Conversion of N-Acetyl Trimethyl β-Chondrosaminide into its α-Isomer.—The β-chondrosaminide (0·2 g.) was dissolved in 25 c.c. of 1% methyl-alcoholic hydrogen chloride, and the solution boiled for 8 hours; $[\alpha]_D^{21°}$ +7° → $[\alpha]_D^{21°}$ +110°. The hydrochloric acid was neutralised by addition of lead carbonate, and the filtered solution evaporated to dryness. The solid residue (0·2 g.) was recrystallised from ethyl acetate–light petroleum, giving white needles, m. p. and mixed m. p. with the α-form previously described, 185°; $[\alpha]_D^{20°}$ +120° in chloroform (*c*, 1·0).

Triacetyl N-Acetyl Chondrosamine.—Amorphous penta-acetyl chondrosamine (3 g.) was dissolved in glacial acetic acid (30 c.c.) saturated with hydrogen bromide. After being kept for 4 hours, the liquid was dissolved in chloroform, and the solution washed with water until free from acid. The dried chloroform solution was concentrated to a syrup which slowly crystallised. Recrystallised from ethyl alcohol–light petroleum, the crystals had m. p. 152° and consisted essentially of acetobromochondrosamine (Found: Br, 17·1. Calc. for $C_{14}H_{20}O_8NBr$: Br, 19·5%). The bromine in this compound was relatively labile, since on recrystallising the above material several times from 90% aqueous ethyl alcohol a bromine-free product, m. p. 183°, $[\alpha]_D^{20°}$ +60° in chloroform (*c*, 1·0), was obtained (Found: C, 46·4; H, 6·2; N, 3·6. *Triacetyl N-acetyl chondrosamine monohydrate*, $C_{14}H_{21}O_9N,H_2O$ requires C, 46·0; H, 6·3; N, 3·8%).

Hydrolysis of N-Acetyl Trimethyl α-Methylchondrosaminide.—This compound (1·0 g.) was dissolved in N-hydrochloric acid (60 c.c.) and heated on the boiling water-bath until hydrolysis was complete ($[\alpha]_D^{21°}$ +139° ⟶ 112° in 4 hours). The solvent was distilled off under diminished pressure, and the residue partly crystallised (0·5 g.); recrystallised from alcohol–ether, it had m. p. 178°, $[\alpha]_D$ +114° equilibrium value in water (*c*, 1·0) (Found: Cl, 13·5; OMe, 36·0. Calc. for trimethyl chondrosamine hydrochloride, $C_9H_{20}O_5NCl$: Cl, 13·8; OMe, 36·1%). Attempts to prepare the free amine gave unstable liquids.

The author thanks Professor W. N. Haworth, F.R.S., for his interest in this work.

A. E. Hills Laboratories,
The University, Edgbaston, Birmingham.

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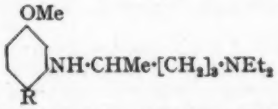
73. *Some Basically Substituted Derivatives of Benziminazole and Lupinane.*

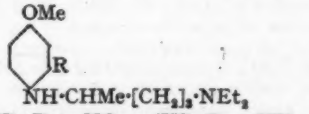
By G. R. Clemo and G. A. Swan.

The preparation of 1-(ε-diethylamino-β-pentyl)benziminazole derivatives carrying a methoxyl group in the 5- or 6-position, with or without a methyl group in the 2-position of the nucleus, is recorded. 11-(ε-Diethylamino-β-pentyl)aminolupinane has also been prepared.

The preparation of 4-nitro-3-(ε-diethylamino-β-pentyl)aminoanisole (I) by condensation of δ-amino-α-diethylaminopentane with 3 : 4-dinitroanisole is described by Topeijev (*Compt. rend. Acad. Sci. U.R.S.S.*, 1935, **4**, 201), although the evidence put forward to prove that replacement occurs in the 3- rather than the 4- position is not conclusive. However, we have obtained the same condensation product by using 3-bromo-4-nitro-



(I), R = NO_2. (II), R = NH_2.

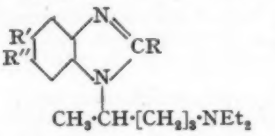


(III), R = NO_2. (IV), R = NH_2.

instead of 3 : 4-dinitro-anisole; but from the preparative point of view, Topeijev's method is superior. Reduction of (I) gives the corresponding derivative of 3-aminoanisole (II). We have also carried out the condens-

ation with 4-bromo-3-nitroanisole, and obtained 3-*nitro*-4-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (III), which, on reduction, gave the corresponding 3-*amino*-compound (IV).

By condensing (II) and (IV) with anhydrous formic acid or acetic anhydride, the benziminazole *derivatives* (V)—(VIII) were obtained. The compounds (I)—(VIII) are all oils, but whereas (I)—(IV) fail to give



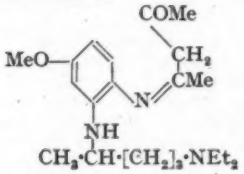
(V), R, R′ = H; R″ = OMe. (VI), R = Me; R′ = H; R″ = OMe.

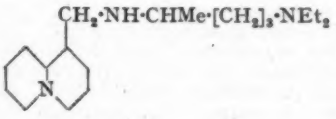
(VII), R, R″ = H; R′ = OMe. (VIII), R = Me; R′ = OMe; R″ = H.

crystalline picrates or picrolonates, the benziminazole compounds (V)—(VIII) give highly crystalline derivatives of sharp melting point. By making use of the latter, we have definitely established the identity of the products of the reaction of δ-amino-α-diethylaminopentane with 3 : 4-dinitro- and with 3-bromo-4-nitroanisole.

Attempts to condense (II) with acetylacetone, with a view to obtain a plasmoquin-like compound with methyl groups substituted in the 2- and the 4-position of the quinoline nucleus, gave only an oil which appears to be the Schiff's base (IX).

(IX.)





(X.)

Condensation of δ-amino-α-diethylaminopentane with 11-bromolupinane gave 11-(ε-diethylamino-β-pentyl)aminolupinane (X). Biological tests show that these compounds are without action on avian malaria.

Experimental.

Preparation of 4-*Nitro*-3-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (I).—Method I. 3-Bromo-4-nitroanisole was prepared as follows. 3-Bromo-4-nitrophenol (11 g.) (Hodgson and Crook, J., 1936, 1677) was dissolved in dry xylene (200 c.c.); sodium bicarbonate (40 g.) and freshly purified methyl sulphate (19 c.c.) were added, the mixture stirred at 120° for 6 hours and cooled, and water added. The xylene layer was separated, washed (dilute sodium hydroxide solution), dried (sodium sulphate), the xylene removed in a vacuum, and the residue crystallised from light petroleum; yield, 11·3 g.; m. p. 45°.

This compound (4 g.), δ-amino-α-diethylaminopentane (7·2 c.c.), and a trace of copper powder were heated together in a sealed tube for 10 hours in the water-bath. Dilute sodium carbonate solution was then added, the excess of pentane base removed by steam-distillation, and the alkaline solution extracted with ether. The extract was shaken with dilute hydrochloric acid, the base reprecipitated from the acid extract by addition of sodium hydroxide solution, taken up in ether, dried with potassium carbonate, and distilled (2·5 g., b. p. 200—205°/1·5 mm.).

Method II. 3 : 4-Dinitroanisole was prepared from 3-nitro-*p*-anisidine by Topeijev's method (*loc. cit.*) (yield, 65%). This compound (3·5 g.) was mixed with δ-amino-α-diethylaminopentane (5 c.c.) and gradually heated under reflux in an oil-bath. When the temperature reached 80°, a violent reaction suddenly began; after this had subsided, the mixture was heated at 145° for 8 hours, cooled, sodium carbonate solution added, and the product worked up as in method (I), giving 4 g., b. p. 205°/2 mm.

The reduction to 4-amino-3-(ε-diethylamino-β-pentyl)aminoanisole (II) was carried out by Topeijev's method (*loc. cit.*).

3-*Nitro*-4-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (III).—4-Bromo-3-nitroanisole (11·5 g.) (Hodgson, J., 1935, 947), δ-amino-α-diethylaminopentane (20 c.c.), and a trace of copper powder were heated together in a sealed tube for 9 hours at 140°. Sodium carbonate solution was added to the product, and the excess of pentane base removed by steam-distillation. After cooling, the non-volatile oil was taken up in ether, the basic material extracted from the ether with dilute acetic acid, the acid extract basified (sodium hydroxide solution), and extracted with ether. After drying (potassium carbonate), the ether was removed, and the residue distilled, giving the *base* as a red, viscous oil (2·8 g., b. p. 195—200°/2 mm.) (Found : C, 62·8; H, 8·75. $C_{16}H_{27}O_3N_3$ requires C, 62·1; H, 8·75%).

The above steam-distillate was acidified (hydrochloric acid), evaporated on the water-bath to a thick gum, and basified (40% sodium hydroxide solution), and the pentane base separated, dried, and distilled, giving 10 g. of pure compound.

3-*Amino*-4-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (IV).—To a cooled solution of the above nitro-compound (2·7 g.) in concentrated hydrochloric acid (7 c.c.), stannous chloride (7 g. of dihydrate) in concentrated hydrochloric acid (10 c.c.) was gradually added with shaking. After standing overnight, excess of sodium hydroxide solution was added, the product extracted with ether, the extract dried (potassium carbonate), the ether removed, and the residue distilled, giving the *base* (IV) as a pale yellow, viscous oil (1·55 g., b. p. 180—185°/2 mm.) (Found : C, 68·6; H, 10·45. $C_{16}H_{29}ON_3$ requires C, 68·8; H, 10·4%).

1-(ε-*Diethylamino*-β-*pentyl*)-6-*methoxybenziminazole* (V).—4-Amino-3-(ε-diethylamino-β-pentyl)aminoanisole (1·9 g.) was heated with anhydrous formic acid (2 c.c.) for 2 hours at 165°. After cooling, the product was dissolved in water, basified (sodium hydroxide), extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue distilled in a vacuum (yield 0·91 g.). A solution of this base in methanol was added to a hot, saturated solution of picrolonic acid (2 mols.) in the same solvent; on cooling, crystals of the *dipicrolonate* (1·8 g., m. p. 193°) separated. Recrystallisation from acetone–methanol raised the m. p. to 197° (Found : C, 54·0; H, 4·9. $C_{17}H_{27}ON_3,2C_{10}H_8O_5N_4$ requires C, 54·35; H, 5·25%). The picrolonate (1 g.) was ground with warm, concentrated hydrochloric acid, the precipitated picrolonic acid filtered off, and the filtrate basified (sodium hydroxide), and extracted with ether. The extract was dried with potassium carbonate, the ether removed, and the residue distilled, giving the *base* (V) as a pale yellow oil (0·29 g., b. p. 190°/1·5 mm.) (Found : C, 70·1; H, 9·55. $C_{17}H_{27}ON_3$ requires C, 70·55; H, 9·35%). The picrate, recrystallised from methanol, had m. p. 135°.

1-(ε-*Diethylamino-β-pentyl*)-6-*methoxy*-2-*methylbenziminazole* (VI).—4-Amino-3 (ε-diethylamino-β-pentyl)aminoanisole (1·1 g.) was heated with acetic anhydride (2 c.c.) for 5 hours at 165°, and the product (1 g.) worked up as before. This crude base gave 1·8 g. of *dipicrolonate*, m. p. 230° (Found, on material crystallised from acetone–methanol: C, 55·0; H, 5·5. $C_{18}H_{29}ON_3,2C_{10}H_8O_5N_4$ requires C, 54·9; H, 5·4%). The free *base* (0·3 g., b. p. 190°/1·5 mm.) recovered from the pure picrolonate (0·95 g.) was a pale yellow, viscous liquid (Found: C, 71·25; H, 9·8. $C_{18}H_{29}ON_3$ requires C, 71·3; H, 9·6%). The picrate had m. p. 192°.

This preparation was carried out with specimens of the starting material prepared from 3-bromo-4-nitroanisole by method (I) and from 3 : 4-dinitroanisole by method (II). The picrate and picrolonate prepared from each product were indistinguishable, and no depression of m. p. was observed on admixture. Depression of m. p. was, however, observed on admixture with the corresponding derivatives of 4-bromo-3-nitroanisole.

1-(ε-*Diethylamino-β-pentyl*)-5-*methoxybenziminazole* (VII).—3-Amino-4-(ε-diethylamino-β-pentyl)aminoanisole (1·5 g.) was heated with anhydrous formic acid (3 c.c.) for 3 hours at 165°, and the product (1·1 g.) worked up as before. Its solution in methanol was added to a hot solution of picric acid (2 mols.) in methanol. After cooling, the crude *picrate* (m. p. 150° approx.) was filtered off and recrystallised from acetone–methanol (1·55 g.; m. p. 161°) (Found: C, 46·4; H, 4·55. $C_{17}H_{27}ON_3,2C_6H_3O_7N_3$ requires C, 46·6; H, 4·4%). The free *base* (0·43 g.; b. p. 195°/2 mm.), recovered from the pure picrate (1·5 g.) as described for the decomposition of the picrolonates, was a pale yellow, viscous liquid (Found: C, 70·7; H, 9·55. $C_{17}H_{27}ON_3$ requires C, 70·55; H, 9·35%).

1-(ε-*Diethylamino-β-pentyl*)-5-*methoxy*-2-*methylbenziminazole* (VIII).—3-Amino-4-(ε-diethylamino-β-pentyl)aminoanisole (1·55 g.) was heated with acetic anhydride (2·7 c.c.) for 5 hours at 165°, and the product (1·34 g.) worked up as before. This crude base gave 2 g. of *dipicrate*, which by recrystallisation from acetone–methanol gave 1·2 g., m. p. 198° (Found: C, 46·9; H, 4·65. $C_{18}H_{29}ON_3,2C_6H_3O_7N_3$ requires C, 47·3; H, 4·6%). On decomposition, this pure picrate gave the *base* (0·3 g.; b. p. 195°/2 mm.) as a viscous liquid (Found: C, 70·6; H, 9·65. $C_{18}H_{29}ON_3$ requires C, 71·3; H, 9·55%). The picrolonate had m. p. 229°.

11-(ε-*Diethylamino-β-pentyl*)*aminolupinane* (X).—11-Bromolupinane (1·3 g.) (Clemo, Raper, and Tenniswood; J., 1931, 433), δ-amino-α-diethylaminopentane (1·7 c.c.), and a trace of copper powder were heated together in a sealed tube for 20 hours in the water-bath. After the addition of sodium carbonate solution, the excess of pentane base was removed by steam-distillation, the non-volatile base extracted with ether, the extract dried with potassium carbonate, the ether removed, and the product distilled (yield 1·02 g., b. p. 165—167°/2 mm.). When this base was mixed with picrolonic acid (3 mols.) in warm, dilute methanol, and the mixed solution allowed to cool slowly, the *tripicrolonate* (m. p. 166—172° approx.) separated slowly (Found: C, 53·1; H, 6·25; N, 19·25. $C_{19}H_{33}N_3,3C_{10}H_8O_5N_4$ requires C, 53·4; H, 5·7; N, 19·05%). On decomposition in the usual way, this gave the free *base*, as an almost colourless liquid (b. p. 165—167°/2 mm.) (Found: C, 73·75; H, 12·9. $C_{19}H_{39}N_3$ requires C, 73·8; H, 12·6%).

Condensation of 4-*Amino*-3-(ε-*diethylamino-β-pentyl*)*aminoanisole with Acetylacetone*.—The base (0·8 g.) and acetylacetone (0·3 g.) were mixed and gently warmed, and the mixture kept for 14 hours at room temperature. Sulphuric acid (4 c.c., *d* 1·8) was then added, the mixture heated for one hour on the water-bath, cooled, and poured into ice-water. After basification (sodium hydroxide), the product was extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue distilled, affording 0·4 g. of the *base* as a yellow, viscous oil, b. p. 175°/1·5 mm. (Found: C, 69·3; H, 9·75. $C_{21}H_{35}O_2N_3$ requires C, 69·8; H, 9·7%).

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KING'S COLLEGE, NEWCASTLE-UPON-TYNE, UNIVERSITY OF DURHAM. [*Received, March 7th*, 1944.]

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74. *The Stereochemistry of Organic Derivatives of Phosphorus. Part I. The Synthesis of Acidic and Basic Dissymmetric Tertiary Phosphines. The Optical Resolution of Phenyl-*p*-(carboxymethoxy)phenyl-*n*-butylphosphine Sulphide.*

By W. CULE DAVIES and FREDERICK G. MANN.

An account is given of the new methods developed for the synthesis of tertiary phosphines in which the phosphorus atom is linked to three unlike alkyl or aryl groups, one of which also carries an acidic or basic group for subsequent salt formation. The oxides, sulphides, and selenides * of such compounds, of the type abcP→S, should be susceptible to optical resolution. The resolution of one such compound, phenyl-*p*-(carboxymethoxy)phenyl-*n*-butylphosphine sulphide (XV), is described. The *d*- and the *l*-form of this acid, having $[M]_D$ +9·6° and −9·7°, have been isolated by the fractional crystallisation of the *l*- and *d*-α-phenylethylamine salts, respectively.

ALTHOUGH there is now considerable physical evidence for the configuration of derivatives of 3- and 4-covalent phosphorus, there is a remarkable paucity of independent chemical evidence for such configurations. Chemical investigations have been directed almost exclusively to the attempted optical resolution of suitable derivatives of 4-covalent phosphorus. Such resolution, if successful, would have shown that the phosphorus atom and the four attached groups could not be uniplanar, and therefore that the phosphorus atom probably (but not necessarily) had a tetrahedal configuration. These derivatives fall mainly into three distinct classes.

(A) *Phosphoric and Phosphonic Acids*.—Early attempts to resolve substituted phosphoric acids, of type (NHR)(NHR')(OH)P→O and (OR)(OR')(OH)P→O (Caven, J., 1902, **81**, 1362; Luff and Kipping, J., 1909, **95**, 1993), and phosphonic acids, of type RR'(OH)P→O (Pope and Gibson, J., 1912, **101**, 740), are now known to have been fore-doomed to failure, as resonance in the phosphorus anion makes the phosphorus atom symmetric. The *d*-hydrindamide of phenyl-*p*-tolylphosphoric acid, (OPh)(OTol)(C_9H_9NH)P→O,

* Interatomic distances indicate that in these oxides and sulphides (and presumably therefore in the selenides also), the bond joining the phosphorus to the Group 6 element is a resonance hybrid between a double bond and a co-ordinate link. Since there is no symbol for such a bond, the → symbol is used conventionally throughout this paper. The precise nature of this covalent link does not, of course, affect the stereochemical considerations underlying our work.

was separated into diastereoisomerides (Luff and Kipping, *loc. cit.*) but an optically active acid could clearly not be obtained by removing the hydrindamine residue (see also Kipping and Challenger, J., 1911, **99**, 626). It is noteworthy that Hatt (J., 1933, 776) separated ethyl triphenylmethylpyrophosphonate, $Ph_3C{-}P(O)(OEt){-}O{-}P(O)(OEt){-}CPh_3$, into two forms, m. p. 222—223° and 228—231°, one of which must have been the racemic and the other the *meso*-form: both forms on hydrolysis necessarily gave the same acid, in which of course ionisation and resonance caused each phosphorus atom to become symmetric.

(B) *Phosphonium Salts.*—It is a striking fact that no phosphonium salt of type [abcdP]X, where a, b, c, d are different alkyl or aryl groups and X is a univalent acid radical, has yet been resolved (cf. Michaelis, *Annalen*, 1901, **315**, 54; Pope and Gibson, *loc. cit.*, p. 735; Wedekind, *Ber.*, 1912, **45**, 2933; Radcliffe and Brindley, *Chem. and Ind.*, 1923, **42**, 64; Meisenheimer *et al.*, *Annalen*, 1926, **449**, 224; Kamai, *J. Gen. Chem. Russ.*, 1932, **2**, 526). This failure is due partly to the great experimental difficulties in synthesising and isolating suitable crystalline compounds, but possibly also to some more fundamental and still unknown factor. All phosphonium salts investigated have had at least one alkyl group, and may therefore have given a "dissociation-equilibrium," $[abcdP]X \rightleftharpoons abcP + dX$, in solution, a process known to occur with quaternary ammonium and arsonium salts (cf. Burrows and Turner, J., 1921, **119**, 426; Davies and Cox, J., 1937, 614; Holliman and Mann, J., 1943, 550) and which would cause rapid racemisation: Wedekind (*loc. cit.*) has, however, adduced some evidence that phosphonium salts do not so dissociate in solution. The critical test would be the attempted resolution of a phosphonium salt in which a, b, c, d were unlike aryl radicals, and in which this dissociation could not occur. The synthesis of such a salt, now possible by Chatt and Mann's reaction (J., 1940, 1192), will be undertaken directly conditions permit.

(C) *Tertiary Phosphine Oxides, Sulphides, and Selenides.*—The only complete resolution of a 4-covalent phosphorus compound was achieved by Meisenheimer *et al.* (Ber., 1911, **44**, 356; *loc. cit.*), who resolved compounds of type $abcP{\rightarrow}O$ through their camphor- and bromocamphor-sulphonates. Meisenheimer's method has two disadvantages: (i) experimental difficulties (due mainly to retarded crystallisation) entailed over 15 years' work to obtain a satisfactory resolution, (ii) the polar $P{\rightarrow}O$ linkage was utilised for combination with the optically active sulphonic acids, and the method cannot therefore be applied to the corresponding sulphides and selenides.

We wished to prepare and resolve three similar compounds, $abcP{\rightarrow}O$, $abcP{\rightarrow}S$, $abcP{\rightarrow}Se$, and then to compare their rotatory dispersions. For this purpose, therefore, one of the radicals, a, b, or c had to carry an acidic or basic group for subsequent salt formation. The object of this paper is primarily to describe the new synthetic methods developed for preparing such compounds, and to record the initial resolution of one compound, *phenyl*-p-(*carboxymethoxy*)*phenyl*-n-*butylphosphine sulphide* (XV).

In our first experiments, *p*-bromophenyldichlorophosphine (I) was converted by diphenylmercury into *phenyl*-p-*bromophenylchlorophosphine* (II), a liquid which was characterised by its ready conversion into *phenyl*-p-*bromophenylphosphonic acid*, $Ph(C_6H_4Br)(OH)P{\rightarrow}O$. *p*-Bromodimethylaniline will not form a Grignard

$(C_6H_4Br)Cl_2P$ (I.) $\longrightarrow$ $Ph(C_6H_4Br)ClP$ (II.) $\longrightarrow$ $Ph(C_6H_4Br)(C_6H_4{\cdot}NMe_2)P$ (III.) $\longrightarrow$ $Ph(C_6H_4Br)(C_6H_4{\cdot}NMe_2)P{\rightarrow}S$ (IV.) $\longrightarrow$ $Ph(C_6H_4Br)(C_6H_4{\cdot}NMe_2I)\,P{\rightarrow}S$ (V.)

(II.) $\longrightarrow$ $Ph(C_6H_4Br)(2\text{-py})P$ (VI.) $\longrightarrow$ $Ph(C_6H_4Br)(2\text{-py})P{\rightarrow}S$ (VII.) $\longrightarrow$ $Ph(BrC_6H_4)(2\text{-pyMeI})P{\rightarrow}S$ (VIII.)

reagent under normal conditions; ultimately, however, we obtained this reagent by Grignard's "entrainment" method (*Compt. rend.*, 1934, **198**, 625, 2217), magnesium being boiled with a mixed ethereal solution of ethyl bromide and *p*-bromodimethylaniline. This reagent reacted readily with the chlorophosphine (II) to give *phenyl*-p-*bromophenyl*-p-*dimethylaminophenylphosphine* (III), colourless crystals, m. p. 107—108°, which by direct union gave the corresponding *phosphine sulphide* (IV) and *selenide*. In later experiments, the phosphine (III) was obtained by using the lithium derivative of *p*-bromodimethylaniline, which is more readily prepared and even more reactive than the corresponding Grignard reagent.

The phosphine sulphide (IV) was too weakly basic for stable salt formation: it also reacted only very sluggishly with methyl iodide, but finally, by working in nitromethane solution, the crystalline *methiodide* (V) was isolated. This iodide in turn gave the crystalline *metho*-d-*camphorsulphonate* and *metho*-d-α-*bromocamphorsulphonate*, but these salts after repeated crystallisation gave no evidence of resolution, each with calcium bromide giving the inactive *methobromide*. The metho-*d*-camphornitronate was also prepared, but only as a glassy substance that could not be obtained crystalline.

In view of these results, it was decided to introduce the 2-pyridyl group into the phosphine for salt formation. By again utilising the entrainment method, 2-pyridylmagnesium bromide was prepared (Overhoff and Proost, *Rec. Trav. chim.*, 1938, **57**, 179), although the corresponding lithium derivative could not be obtained. This Grignard reagent reacted with the chlorophosphine (II), giving *phenyl*-p-*bromophenyl*-2-*pyridylphosphine* (VI), m. p. 90—91°, which then gave the *sulphide* (VII). The 2-pyridyl group in (VII) proved, however, so weakly basic that the sulphide crystallised unchanged from an alcoholic solution of *d*-camphorsulphonic acid and from an aqueous-acetone solution of *d*-bromocamphorsulphonic acid. The sulphide was also unaffected by boiling in methyl iodide for 2 hours, but when heated with excess of methyl iodide at 100° it underwent complete disruption, forming tetramethylphosphonium iodide in almost theoretical yield; prolonged exposure

to methyl iodide in warm nitromethane solution gave, however, the *methiodide* (VIII) of the phosphine sulphide, but only in very low yield. In view of these difficulties, work on derivatives of (VIII) was discontinued.

Since it appeared probable that the weakly basic properties of the 2-pyridyl group in the sulphide (VII) were due to the close proximity of the nitrogen and the phosphorus atom, the distance between these atoms was increased by preparing the isomeric 3-pyridyl derivative. A Grignard reagent was obtained with difficulty from 3-bromopyridine, and when treated with the chlorophosphine (II) it furnished phenyl-*p*-bromophenyl-3-pyridylphosphine, which was characterised as its crystalline *picrate*. This phosphine readily gave the *phosphine sulphide*, but the nitrogen atom in this compound was even more feebly basic than that in the 2-pyridyl isomeride, and the sulphide would not combine with camphorsulphonic or bromocamphorsulphonic acid, nor could a methiodide be prepared. It is noteworthy that whereas picrates were readily formed by both the 2-pyridylphosphine (VI) and its 3-pyridyl isomeride, such salts could not be obtained from the corresponding phosphine sulphides. This deactivation of the tertiary nitrogen atom accompanying increased covalency of the phosphorus atom is being separately studied.

The synthesis of dissymmetric tertiary phosphine sulphides containing an acidic group was now investigated. The general method visualised was the preparation of a tertiary phosphine containing a *p*-anisyl radical, its demethylation to the *p*-hydroxyphenylphosphine, and the condensation of the sodium salt of the latter with ethyl bromoacetate to give finally the *p*-(carboxymethoxy)phenylphosphine:

$$(C_6H_4{\cdot}OMe)R^1R^2P \longrightarrow (C_6H_4{\cdot}OH)R^1R^2P \longrightarrow (C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CO_2H)R^1R^2P$$

No tertiary phosphine containing a hydroxyphenyl radical had previously been prepared, however; furthermore, in the arsine series Michaelis and Weitz (*Ber.*, **1887**, **20**, 48) had shown that warm hydriodic acid decomposed tri-*p*-anisylarsine into anisole and the dianisyliodoarsine, and more vigorous treatment decomposed it into anisole and arsenic tri-iodide. To test our proposed synthesis, therefore, *p*-anisyldichlorophosphine (IX) was converted into *p*-anisyldiethylphosphine, which under suitable treatment with hydriodic acid underwent smooth conversion into p-*hydroxyphenyldiethylphosphine*, the first phosphine of this type to be isolated: this phosphine gave a highly crystalline *methiodide*.

In view of this encouraging result, the dichlorophosphine (IX) was converted by diphenylmercury into *phenyl*-p-*anisylchlorophosphine* (X) and the latter by a Grignard reagent into *phenyl*-p-*anisyl*-n-*butylphosphine* (XI). This phosphine was demethylated with hydriodic acid. The crude, viscous product was apparently the hydriodide $Ph(C_6H_4{\cdot}OH)BuP,HI$, which with sodium carbonate gave a compound whose properties indicated zwitterion formation, $Ph(C_6H_4{\cdot}\overset{-}{O})Bu\overset{+}{P}H$; the reaction product was therefore benzoylated in caustic alkaline suspension to furnish the crystalline p-*benzoyloxyphenylphosphine* (XII). The latter united readily with sulphur to form the *phosphine sulphide* (XIII), which on alkaline hydrolysis gave the highly crystalline *phenyl*-p-*hydroxy*-

$$\underset{\text{(IX.)}}{(C_6H_4{\cdot}OMe)Cl_2P} \longrightarrow \underset{\text{(X.)}}{Ph(C_6H_4{\cdot}OMe)ClP} \longrightarrow \underset{\text{(XI.)}}{Ph(C_6H_4{\cdot}OMe)BuP} \longrightarrow \underset{\text{(XII.)}}{Ph(C_6H_4{\cdot}OBz)BuP}$$

$$\longrightarrow \underset{\text{(XIII.)}}{Ph(C_6H_4{\cdot}OBz)BuP{\rightarrow}S} \longrightarrow \underset{\text{(XIV.)}}{Ph(C_6H_4{\cdot}OH)BuP{\rightarrow}S} \longrightarrow \underset{\text{(XV.)}}{Ph(C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CO_2H)BuP{\rightarrow}S}$$

phenyl-n-*butylphosphine sulphide* (XIV). An alcoholic solution of the sodium derivative of this hydroxy-compound (XIV) condensed readily with ethyl bromoacetate, and the product on alkaline hydrolysis yielded the crude sodium salt of the carboxymethoxy-phosphine sulphide (XV). This salt without purification was treated in alcoholic solution with *d*-α-phenylethylamine hydrochloride, and the highly crystalline d-α-*phenylethylamine* salt of *phenyl*-p-(*carboxymethoxy*)*phenyl*-n-*butylphosphine sulphide* (XV) separated. This salt had originally m. p. 195—201°, but fractional crystallisation from alcohol caused a steady rise in m. p. and ultimately gave the optically pure *d*-amine *l*-acid, m. p. 209—210°. The latter salt, when decomposed by dilute sulphuric acid, furnished the *l*-phenyl-*p*-carboxymethoxyphenyl-*n*-butylphosphine sulphide, having $[M]_D$ −9·7° in benzene solution. Further crystallisation of the amine-salt did not change its m. p. or increase the rotation of the liberated phosphine sulphide acid. The *l*-acid gave a l-*ammonium* salt which was freely soluble in water, but its complete rotatory dispersion has not yet been measured owing to temporary lack of facilities. The following values in the visible spectrum, for a 4·770% aqueous solution of the ammonium salt, show clearly, however, that it possesses complex anomalous rotatory dispersion, which is not unexpected in view of its structure:

Wave-length of light, A.	6708	6104	5893	5780	5461	5086	4358
$[M]$	−9·6°	−10·5°	−10·7°	−11·9°	−11·5°	−8·2°	−0·6°

The acid recovered from the earlier mother-liquors of the above fractional crystallisations was now converted into the l-α-*phenylethylamine* salt of the d-*acid*, which had at first m. p. 193—200°, raised by fractional crystallisation to 209—210°. From this salt, the free *d*-phosphine sulphide acid (XV) was obtained, having $[M]_D$ +9·6° in benzene solution; this in turn furnished the d-*ammonium* salt, a 3·142% aqueous solution of which had $[M]_{5893}$ +11·3°, $[M]_{5461}$ +12·2°. The rotation of the ammonium salt is therefore dependent on the concentration of the solution.

It is noteworthy that the crystalline *ethyl* homologue of the acid (XV), *i.e.*, $Ph(C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CO_2H)EtPS$, in the preparation of which we were kindly assisted by Mr. J. Harley-Mason, gave well characterised *salts* with

l-α-phenylethylamine, *d*-*sec*.-butylamine, and *d*-α-aminocamphor, but none of these salts after repeated crystallisation furnished any evidence of optical resolution.

Certain other points arising in this investigation deserve brief mention. We have utilised some of the above phosphines to prepare *phenyl*-p-*anisylmethylethylphosphonium* and *phenyl*-p-*anisylethyl*-n-*propylphosphonium iodides*, and *phenyl*-p-*anisyl*-p-*tolyl*-p-*chlorophenacylphosphonium bromide*. From none of these salts, however, could we isolate a crystalline *d*-camphorsulphonate or *d*-α-bromocamphorsulphonate.

We have also utilised two of our dissymmetric tertiary phosphines to prepare *dichlorobis*(*phenyl*-p-*bromophenyl*-p-*dimethylaminophenylphosphine*)*palladium* (XVI) and *dichlorobis*(*phenyl*-p-*bromophenylethylphosphine*)-*palladium* (XVII). Both these compounds would undoubtedly have only the *trans*-configuration. Each,

(XVI.) $[\{Ph(C_6H_4Br)(C_6H_4\cdot NMe_2)P\}_2PdCl_2]$ $[\{Ph(C_6H_4Br)EtP\}_2PdCl_2]$ (XVII.)

however, contains two similar asymmetric 4-covalent phosphorus atoms and therefore could exist in two forms, *meso* and racemic, similar to the two forms of ethylene-αβ-bis(phenylbutylarsine)dichloropalladium isolated by Chatt and Mann (J., 1939, 1625). The compound (XVI) was too slightly soluble for effective fractional crystallisation but (XVII) was crystallised repeatedly; it appeared, however, to be homogeneous, and no indication of two forms was detected.

The reagent, 2-pyridylmagnesium bromide, used in the synthesis of the phosphine (VI), has also been used to prepare the crystalline *tri*-2-*pyridylphosphine* and *tri*-2-*pyridylarsine*. A detailed investigation of the chemical and therapeutic properties of these novel types of tertiary phosphine and arsine is now in progress.

Experimental.

The names of solvents used for recrystallisation are given in parenthesis immediately after the names of the compounds concerned. All rotations were determined in a 4-dcm. tube at 16° ± 1°, sodium-*D* light ($\lambda = 5893$) being used unless otherwise stated.

p-*Bromophenyldichlorophosphine* (I).—A mixture of bromobenzene (400 c.c.), phosphorus trichloride (500 c.c., 1·5 mols.), and aluminium chloride (120 g., 0·24 mol.) was refluxed for 48 hours. The cold product was extracted with petrol (b. p. 60—80°; 650 c.c.), and the petrol and excess trichloride then removed, and the residue fractionally distilled at reduced pressure. The phosphine (I) was collected, b. p. 136—142°/13 mm. (69 g.), and then refractionated: b. p. 139°/13 mm., 147—148°/21 mm. (cf. Michaelis, *Annalen*, 1896, **293**, 237).

Phenyl-p-*bromophenylchlorophosphine* (II).—A mixture of the phosphine (I; 98 g.) and powdered diphenylmercury (85 g.; 0·63 mol.) was heated at 210° for 1½ hours in a nitrogen atmosphere. The cold product was vigorously shaken with petrol (b. p. 60—80°; 200 c.c.), filtered at the pump, and the undissolved residue thoroughly washed on the filter with more petrol. The united extract and washings were distilled, the solvent at normal pressure and the residue under reduced pressure; a fraction of crude unchanged dichlorophosphine (b. p. 120—190°/11 mm.) was collected, and then the crude chlorophosphine, b. p. 195—215°/11 mm.; the latter, on redistillation, gave the pure *phosphine* (II), b. p. 203—204°/11 mm., 35—40 g. (Found: C, 47·9; H, 3·2; Cl + Br, 38·4. $C_{12}H_9ClBrP$ requires C, 48·1; H, 3·0; Cl + Br, 38·5%).

The early fraction, b. p. 120—190°/11 mm., on refractionation gave a large quantity of unchanged (I), b. p. 135—143°/11 mm., and a small quantity of crude (II), b. p. 195—215°/11 mm.

When chlorine was passed over a shallow agitated layer of the phosphine (II), the yellow solid trichloride, $Ph(C_6H_4Br)Cl_2P$, was rapidly formed. This was decomposed with cold water, which was subsequently boiled; the solid residue gave *phenyl*-p-*bromophenylphosphonic acid*, colourless crystals (alcohol), m. p. 174·5° (Found: C, 48·8; H, 3·5. $C_{12}H_{10}O_3BrP$ requires C, 48·5; H, 3·4%). The acid is soluble in most organic liquids, but only slightly soluble in boiling water.

Phenyl-p-*bromophenylethylphosphine* was prepared directly for recognition, as it must necessarily arise as a by-product in the preparation of the phosphine (III) when the "entrainment" Grignard reagent is employed. A solution of the chlorophosphine (II; 14 g.) in ether (50 c.c.) was added to a chilled, agitated Grignard reagent prepared from ethyl bromide (10·2 g., 2 mols.), magnesium (3 g.), and ether (150 c.c.). The mixture was refluxed for 30 minutes, cooled, hydrolysed with aqueous ammonium chloride and, after the usual treatment, the *ethylphosphine* was isolated as a colourless liquid, b. p. 136—138°/0·05 mm. (Found: C, 57·9; H, 5·0. $C_{14}H_{14}BrP$ requires C, 57·4; H, 4·8%).

Phenyl-p-*bromophenyl*-p-*dimethylaminophenylphosphine* (III).—(A) *By the Grignard method.* Ethyl bromide (0·8 c.c.) in ether (40 c.c.) was poured on magnesium (11 g.) containing an iodine crystal. When the vigorous reaction ensued, a solution of *p*-bromodimethylaniline (40 g.) and ethyl bromide (6·2 c.c.) in ether (150 c.c.) was added with stirring during 45 minutes, the mixture boiling spontaneously meanwhile. The mixture was refluxed for 2 hours, set aside for 1—2 hours, and finally a solution of the chlorophosphine (II, 20 g.) in benzene (50 c.c.) was added dropwise during 30 minutes to the stirred Grignard reagent, which was kept at 15—20° whilst the moderate interaction occurred. The ether was then distilled off, benzene (200 c.c.) added, and the mixture boiled for 1·5—2 hours and finally cooled in ice, whilst a solution of ammonium chloride (50 g.) in cold water (200 c.c.) was slowly added with vigorous stirring. The benzene layer was separated from the filtered product, the benzene distilled off, and the residue distilled in steam to remove dimethylaniline and *p*-bromodimethylaniline (6—8 g.). The viscous oily residue was dissolved in warm ether, dried, and after removal of the solvent gave the following fractions on distillation at 0·05 mm.: (i) *p*-bromodimethylaniline (trace); (ii) b. p. 100—180°, 4·5 c.c., mainly the above ethyl-phosphine; (iii) b. p. 180—206°, 1 c.c.; (iv) b. p. 206—240° (mainly 218—220°), 11 c.c.; (v) b. p. 240—260°, 0·5 c.c. A solution of the yellow viscous fraction (iv) in a minimum of hot alcohol, when vigorously stirred during spontaneous cooling, deposited the crude *phosphine* (III), 9 g. (37%), which after recrystallisation from alcohol was obtained as colourless crystals, m. p. 107—108° (Found: C, 62·4; H, 4·9; N, 3·8; Br, 20·8. $C_{20}H_{19}NBrP$ requires C, 62·5; H, 5·0; N, 3·7; Br, 20·8%). Fractions (iii) and (v), when mixed with alcohol, slowly deposited more crude phosphine (0·5 g.).

The proportion of reagents used above (chloro-phosphine, 1 mol.; bromo-amine, 3 mols., total ethyl bromide, 1·35 mols., magnesium, 6·75 atoms) ensures an excess of magnesium over the two bromo-compounds, and of the total Grignard reagents over the chloro-phosphine. A blank preparation of the above mixed Grignard reagent showed on analysis (by hydrolysis followed by estimation of dimethylaniline formed) that 60% of the *p*-bromodimethylaniline used had formed a Grignard reagent. The distribution of the chloro-phosphine between the two Grignard reagents will depend on the relative quantities and reactivities of these reagents. It is possible that the reagent from *p*-bromodimethylaniline is more reactive than that from ethyl bromide, for Gilman, St. John, St. John, and Lichtenwalter (*Rec. Trav. chim.*, 1936, **55**, 577, 588) have shown that the Grignard reagent from *p*-bromotoluene is more reactive than that from bromo-

benzene, which in turn is more reactive than that from ethyl bromide. The proportions used above probably approach the optimum.

(B) *By the lithium method.* A piece of clean, ether-washed lithium (0·8 g., 2·9 atoms) was rapidly cut into minute shavings and immediately immersed in dry ether (15 c.c.) contained in the usual reaction vessel fitted with stirrer, reflux condenser, dropping-funnel, and nitrogen inlet tube. A solution of *p*-bromodimethylaniline (10 g., 1·25 mols.) in ether (15 c.c.) was slowly added (20 minutes), the mixture being at first gently warmed to start the reaction, which then continued spontaneously, causing gentle boiling of the solvent. The complete mixture was refluxed for 1 hour, and was then thoroughly chilled, diluted with ether (30 c.c.), and vigorously stirred whilst a solution of the chloro-phosphine (12 g.) in ether (40 c.c.) was added during 1 hour. The mixture, which had become brown and deposited some solid, was set aside for 1 hour, then cooled to 0°, and water (200 c.c.) slowly added. Throughout the whole preparation until this stage, a nitrogen atmosphere was maintained in the apparatus. The ethereal layer was collected, dried (sodium sulphate), the solvent removed, and the yellow oily residue distilled at 0·1 mm. pressure. Two fractions were obtained: (i) b. p. rising to 200° (2 c.c.), mainly dimethylaniline; (ii) b. p. 210—240° (mostly at 230—232°), a pale yellow viscous oil which on dilution with alcohol gave the crystalline phosphine, 7 g. (45%).

Phenyl-p-*bromophenyl*-p-*dimethylaminophenylphosphine Sulphide* (IV).—When solutions of the phosphine (3 g.) and rhombic sulphur (0·25 g., 1 atom), each in carbon disulphide (10 c.c.), were mixed, heat was evolved. The mixture was refluxed for 30 minutes, the solvent evaporated, and the solid residue furnished the colourless *sulphide* (methyl alcohol), m. p. 126° (1·9 g.) (Found: C, 57·8; H, 4·6; N, 3·5. $C_{20}H_{19}NBrSP$ requires C, 57·7; H, 4·6; N, 3·4%). The *methiodide* (V) of this base was best obtained by keeping a mixed solution of the sulphide (6 g.) and methyl iodide (10 c.c.) in nitromethane (25 c.c.) at 40—50° for 3 days; the solid (3·9 g.) which had separated was collected, a second crop (0·8 g.) being obtained by dilution of the filtrate with ether; colourless crystals (methyl alcohol), m. p. 158—159° (Found: C, 45·5; H, 3·9. $C_{21}H_{22}NBrISP$ requires C, 45·2; H, 4·0%). The methiodide is also formed when a solution of the sulphide in methyl iodide is set aside at room temperature for 2—3 days; in ethereal solution, however, little union occurs even after refluxing for 3 days.

The metho-d-camphorsulphonate. The filtrate from mixed hot aqueous methyl-alcoholic solutions of the iodide and of silver camphorsulphonate (1 mol.) was evaporated in a vacuum; the residual oil, dissolved in a minimum of warm acetone, deposited colourless crystals of the *metho-sulphonate*. These, repeatedly recrystallised from methyl alcohol–ether, or acetone–ether, were always obtained as long homogeneous needles of unchanged m. p. (224—226°, decomp.) and rotation (Found: C, 56·1; H, 5·4. $C_{21}H_{23}NBrSP,C_{10}H_{15}O_4S$ requires C, 56·2; H, 5·6%). The lack of resolution was confirmed by mixing cold concentrated methyl-alcoholic solutions of the sulphonate and of calcium bromide; the crystalline *methobromide methyl alcoholate*, m. p. 145°, was collected and thoroughly washed with cold methyl alcohol (Found: C, 48·7; H, 5·3; Br, 29·1. $C_{21}H_{22}NBr_2SP,CH_4O$ requires C, 48·6; H, 4·8; Br 29·4%). It was only slightly soluble in most cold solvents; in diacetone alcohol, in which it was more soluble, it was optically inactive.

The *metho*-d-*α-bromocamphorsulphonate* was similarly obtained as a residual viscous oil which readily crystallised when mixed with ether; colourless crystals, unaffected in rotation by repeated recrystallisation from acetone or methyl alcohol–ether; m. p. 198—199° (Found: C, 49·4; H, 4·6; Br, 21·5. $C_{21}H_{22}NBrSP,C_{10}H_{14}O_4BrS$ requires C, 50·2; H, 4·9; Br, 21·6%). The final crop was also converted into an inactive methobromide as before.

Phenyl-p-*bromophenyl*-p-*dimethylaminophenylphosphine Selenide.*—A solution of the phosphine (III; 2 g.) in carbon disulphide was boiled with powdered selenium (0·45 g.) for 1 hour. The solvent was removed from the filtered solution, and the residue gave the colourless *selenide* (methyl alcohol), m. p. 135·5—136·5° (Found: C, 51·8; H, 4·45. $C_{20}H_{19}NBrSeP$ requires C, 51·9; H, 4·1%).

Phenyl-p-*bromophenyl*-2-*pyridylphosphine* (VI) was prepared by the dropwise addition of a solution of the phosphine (II; 13 g.) in benzene (100 c.c.) to a Grignard reagent prepared by the entrainment method from ethyl bromide (4 c.c. in all), 2-bromopyridine (9·6 c.c.), magnesium (5 g.), and ether (120 c.c.), the method being essentially as for (III) (p. 279). After the removal of the solvent, the residue, on distillation at 0·01 mm. pressure, gave two fractions: (i) b. p. 90—150° (1·5 g.), mainly 2 : 2′-dipyridyl, rapidly solidifying in the receiver, and having m. p. 69—70° after recrystallisation (petrol); (ii) b. p. 160—230°, a viscous liquid. Fraction (ii), on redistillation at 0·01 mm., gave: (iii) b. p. 140—160°, a mobile, pale yellow liquid, mainly the monoethylphosphine; (iv) b. p. 180—230°, a thick viscous liquid. A solution of fraction (iv) in an equal volume of methyl alcohol, set aside at 5°, deposited the crystalline *phosphine* (VI; 2 g.), colourless crystals (methyl alcohol or petrol), m. p. 90—91° (Found: N, 4·35. $C_{17}H_{13}NBrP$ requires N, 4·1%).

To obtain large quantities of (VI), the crude product from a number of such preparations should be united for redistillation: it is inadvisable to increase the above quantities in any one preparation. In our initial preparations, the crystalline phosphine could not be isolated from fraction (iv). The latter in alcoholic solution was therefore treated with methyl-alcoholic picric acid: the precipitated sticky *picrate* solidified on vigorous stirring and ultimately gave yellow leaflets (ethyl alcohol), m. p. 132° (Found: N, 9·8; Br, 14·05. $C_{17}H_{13}NBrP,C_6H_3O_7N_3$ requires N, 9·8; Br, 14·0%). The picrate was decomposed with 10% aqueous sodium hydroxide, and the phosphine, after extraction with ether, was readily recrystallised from methyl alcohol: it was used to seed subsequent solutions of fractions (iv).

The *phosphine sulphide* (VII) was readily obtained from the phosphine (VI; 6 g.) and sulphur (0·6 g.) in carbon disulphide (30 c.c.); colourless crystals (ethyl alcohol), m. p. 109°, 6 g. (Found: C, 54·5; H, 3·55. $C_{17}H_{13}NBrSP$ requires C, 54·6; H, 3·5%). Its *methiodide* (VIII) was best prepared by warming a solution of the sulphide (VII; 2 g.) in methyl iodide (10 c.c.) and nitromethane (20 c.c.) at 50° for 48 hours. The deep red solution was evaporated in a vacuum, and the residual oil scratched to induce crystallisation; washing with ether and 3 recrystallisations from alcohol gave a small yield of the yellow methiodide, m. p. 132—134° (decomp.) (Found: N, 2·6; ionic I, 24·8. $C_{18}H_{16}NBrISP$ requires N, 2·7; I, 24·6%).

The sulphide (VII; 0·3 g.) was unchanged after 2 hours' refluxing with methyl iodide (6 c.c.). Another mixture (VII, 0·5 g.; iodide, 4 c.c.) was heated in a sealed tube at 100° for 4 hours. On cooling, the crystalline product furnished tetramethylphosphonium iodide, colourless crystals (ethyl alcohol), dissociating at 210° (Found: ionic I, 58·2. Calc. for $C_4H_{12}IP$: I, 58·3%).

Methylation with methyl sulphate proved unsatisfactory. The sulphide (VII) was unaffected by heating with excess ethyl iodide at 100° even for 24 hours.

Phenyl-p-*bromophenyl*-3-*pyridylphosphine.*—This was prepared similarly to (VI), a solution of (II; 39 g., 25 c.c.) in benzene (100 c.c.) being added to a Grignard reagent obtained from ethyl bromide (11·5 c.c. in all), 3-bromopyridine (48 g.), magnesium (15 g.), and ether (240 c.c.). The crude residual oil on distillation gave a main fraction, b. p. 190—240°/0·2 mm., which on redistillation gave a small fraction, b. p. 150—195°/0·05 mm., and a larger fraction, b. p. 202—210°/0·15 mm. The latter, clearly the required phosphine, was a viscous, colourless oil which would not solidify. A portion for identification was converted in methyl-alcoholic solution into the *phosphine picrate*, yellow crystals (ethyl alcohol), m. p. 143—144° (decomp.) (Found: C, 47·8; H, 3·27; N, 10·2. $C_{17}H_{13}NBrP,C_6H_3O_7N_3$ requires C, 48·2; H, 3·0; N, 9·8%). The reminder was converted directly into the *phosphine sulphide*, colourless crystals (ethyl alcohol), m. p. 115—116° (Found: C, 54·6; H, 3·5; N, 3·7; Br, 22·0. $C_{17}H_{13}NBrSP$ requires C, 54·5; H, 3·55; N, 3·7; Br, 21·4%).

This sulphide, like the isomeric (VII), was recovered unchanged from alcoholic and acetone solutions of camphor- and bromocamphor-sulphonic acids. Attempts to prepare a methiodide under various conditions gave intractable gums.

p-*Anisyldichlorophosphine* (IX).—The following preparation differs in detail from those of Michaelis (*Annalen*, 1896, **293**, 249) and Jackson, Davies, and Jones (J., 1930, 2298). A mixture of anisole (600 g., 530 c.c.), phosphorus trichloride (760 g., 476 c.c.; 1 mol.), and aluminium chloride (120 g., 0·16 mol.) was refluxed for 36 hours. The cold product was extracted thrice with petrol (b. p. 60—80°), the solvent expelled from the extract, and the residue twice fractionated at reduced pressure; the phosphine (IX) was obtained, b. p. 150°/13 mm., 100 g.

p-*Anisyldiethylphosphine*.—This was originally prepared by Michaelis (*loc. cit.*) by the action of diethylzinc on (IX). We prepared it by adding a solution of (IX; 26 g.) in ether (50 c.c.) dropwise to a chilled, agitated Grignard reagent prepared from ethyl bromide (55 g.), magnesium (12 g.), and ether (300 c.c.). The mixture was refluxed for 30 minutes, and then worked up as usual, the diethylphosphine being obtained as a colourless liquid, b. p. 166—171°/40 mm. (19 g.). The phosphine readily reacts with methyl iodide, giving *p*-anisylmethyldiethylphosphonium iodide (alcohol–ether), m. p. 132—133° (Found: I, 37·5. Calc. for $C_{12}H_{20}OIP$: I, 37·5%): Michaelis (*loc. cit.*) in error gives m. p. 91°.

p-*Hydroxyphenyldiethylphosphine*.—The above phosphine (10 g.) and hydriodic acid of constant b. p. (70 c.c.) were heated together at 135° for 2 hours in a carbon dioxide atmosphere in a Zeisel apparatus. The residual liquid was neutralised with sodium carbonate and extracted with ether; the solvent was removed from the dried, filtered extract, and distillation then gave the crude *phosphine* as a viscous oil, b. p. 168—176°/19 mm. (Found: C, 64·8; H, 9·4. $C_{10}H_{15}OP$ requires C, 65·9; H, 8·3%). As crystallisation of the phosphine was difficult, the latter was united directly with methyl iodide to give p-*hydroxyphenylmethyldiethylphosphonium iodide*, colourless crystals (ethyl alcohol), m. p. 168—169° (Found: C, 40·7; H, 5·8; I, 39·0. $C_{11}H_{18}OIP$ requires C, 40·8; H, 5·6; I, 39·1%). The phosphine also united vigorously with sulphur in carbon disulphide solution, but the phosphine sulphide could not be crystallised.

Phenyl-p-*anisylchlorophosphine* (X).—A mixture of the phosphine (IX; 130 g.) and thoroughly dried diphenylmercury (130 g., 0·6 mol.) was heated rapidly in an oil bath to 175—180°, and kept at this temperature for 1·5 hours. The cold product was repeatedly triturated with petrol (b. p. 60—80°). The united extracts were set aside overnight, separated from a small heavy oily layer, and the petrol removed. The residue, distilled at low pressure, gave first a fraction of crude unchanged (IX), b. p. rising to 120°/0·05 mm., and then the phosphine (X), b. p. 130—140°/0·03 mm., 47 g.; the latter was carefully refractionated, and the pure *phosphine* obtained as a colourless liquid, b. p. 137°/0·03 mm., 149—152°/0·15 mm. (35 g.) (Found: Cl, 14·3. $C_{13}H_{12}OClP$ requires Cl, 14·15%). Distillation of the crude phosphine at water-pump pressures often caused vigorous decomposition.

Phenyl-p-*anisyl*-n-*butylphosphine* (XI).—This was prepared by the action of a solution of the phosphine (X; 60 g.) in ether (100 c.c.) on a Grignard reagent prepared from pure *n*-butyl bromide (76 c.c., 3 mols.) and magnesium (20·4 g., 3·5 atoms) in ether (250 c.c.). After the usual treatment, the *phosphine* (XI) was collected first as a crude fraction, b. p. 132—140°/0·025 mm. (50 g.), and then on refractionation as the pure liquid, b. p. 139—141°/0·025 mm., 176—179°/0·5 mm. (46 g.) (Found: C, 75·5; H, 8·2. $C_{17}H_{21}OP$ requires C, 75·0; H, 7·8%). Isomerisation of a *n*-alkyl group during the conversion of the alkyl halide into the corresponding Grignard reagent is unknown: there is no doubt, therefore, that (XI) contains the *n*-butyl group.

Phenyl-p-*benzoyloxyphenyl*-n-*butylphosphine* (XII).—A mixture of the phosphine (XI; 18 g.) and constant-b. p. hydriodic acid (90 c.c.) was heated at 125—130° for 2·5 hours in a stream of carbon dioxide. The cold product was made alkaline with 20% aqueous sodium hydroxide and immediately shaken with benzoyl chloride (12 c.c.); the crude *benzoyloxy*-compound (XII) (23·5 g.) was rapidly collected. Recrystallisation (ethyl alcohol) gave the pure compound, m. p. 91° (Found: C, 76·5; H, 6·8. $C_{29}H_{29}O_2P$ requires C, 76·2; H, 6·4%). The following points must be noted: (*a*) the use of larger quantities than the above may give difficulties in the subsequent benzoylation; (*b*) the use of sodium carbonate in place of hydroxide does not liberate the hydroxy-phosphine satisfactorily, presumably owing to stable zwitterion formation, $\bar{O}\cdot C_6H_4(Ph)(Bu)\overset{+}{P}H$; (*c*) the crude (XII) should be collected after 10—15 minutes' shaking. Prolonged shaking on one occasion gave the *benzoyloxyphosphine oxide*, white crystals (aqueous alcohol), m. p. 136° (Found: C, 72·75; H, 6·2. $C_{22}H_{23}O_3P$ requires C, 72·95; H, 6·1%).

Sulphide (XIII). A mixture of the phosphine (XII; 18 g.), rhombic sulphur (1·6 g., 1 atom), and alcohol (170 c.c.) was refluxed for 2 hours, allowed to cool spontaneously, and then chilled at 0°. The *sulphide* (XIII) separated as colourless crystals (ethyl alcohol), m. p. 66—67°, 17 g. (Found: C, 69·8; H, 6·0. $C_{29}H_{29}O_3SP$ requires C, 70·0; H, 5·9%): a second crop was obtained by evaporation of the filtrate. The sulphide separates from *cyclo*hexane solution in waxy crystals containing 0·5 mol. of solvent; m. p. 36—38° (Found: C, 71·9; H, 6·8. $C_{29}H_{29}O_2SP,\frac{1}{2}C_6H_{12}$ requires C, 71·5; H, 6·7%); crystallisation from alcohol then gives the pure (XIII), m. p. 66—67°.

The hydroxy-phosphine sulphide (XIV). A mixture of the benzoyloxy-sulphide (XIII; 8 g.), 10% aqueous sodium hydroxide (160 c.c.) and alcohol (30 c.c.), was refluxed until clear (*ca.* 8 hours). The clear solution was cooled, diluted with water (250 c.c.), and saturated with carbon dioxide. The *hydroxy-sulphide* (XIV) separated as a colourless, sticky mass which ultimately disintegrated to a white powder; this, when collected, washed thoroughly with water, and dried, was pure; m. p. 97—98°, unchanged by recrystallisation from *cyclo*hexane (Found: C, 66·2; H, 6·9. $C_{16}H_{19}OSP$ requires C, 66·2; H, 6·6%). Yield almost theoretical.

Phenyl-p-(*carboxymethoxy*)*phenyl*-n-*butylphosphine Sulphide* (XV) *: Preparation and Resolution*.—A solution of the sulphide (XIV; 9 g.) in alcohol (60 c.c.) and ethyl bromoacetate (17·5 c.c., 5 mols.) were added in this order to alcoholic sodium ethoxide (sodium, 2·9 g., 4 atoms; alcohol, 60 c.c.). The mixture was refluxed for 30 minutes, diluted with water (60 c.c.), and the alcohol evaporated on the water-bath, the solution being maintained just alkaline with aqueous sodium hydroxide. The cold concentrated solution, which deposited a small quantity of the viscous sodium salt of (XV), was cautiously acidified with dilute sulphuric acid. The precipitated crude viscous acid (XV) rapidly became semi-solid in the chilled mixture; the aqueous layer was decanted, the residual acid washed with water, dried, dissolved in boiling alcohol (50—60 c.c.), neutralised with alcoholic sodium hydroxide, and treated with a solution of *d*-α-phenylethylamine hydrochloride (4·6 g.) in hot alcohol (20 c.c.). Precipitated sodium chloride was rapidly collected, and the filtrate on cooling readily deposited white crystals of the d-α-*phenylethylamine* salt of the acid (XV): average yield, 5 g.

The *d*-amine salt so obtained, once recrystallised from alcohol, had m. p. 195—201°; eight more recrystallisations from alcohol gave the optically pure d-*amine* l-*carboxy-phosphine sulphide*, m. p. 209—210° (Found: C, 66·6; H, 7·0. $C_{18}H_{21}O_3SP,C_8H_{11}N$ requires C, 66·65; H, 6·9%). This salt was too slightly soluble in cold solvents for reliable rotation measurements to be made. Consequently, 1·5194 g. of it were placed in a small separating-funnel, pure benzene (*ca.* 20 c.c.) added, and the mixture thrice extracted thoroughly with dilute sulphuric acid, great care being taken to avoid any loss of the benzene layer when running off the aqueous layer. The benzene layer was then filtered through a fluted filter-paper, previously moistened with benzene, into a 30 c.c. graduated flask, the funnel being subsequently washed out twice with more benzene which was run through the same filter. The filtrate, when made up to 30 c.c., was now a 3·767% solution of the free *l*-carboxyphosphine sulphide (XV). It had α −0·42°, $[M]$ −9·7°. A portion of the above *d*-amine salt which had been nine times recrystallised was now recrystallised thrice more: its m. p. was unchanged.

1·500 G. of this salt, treated as above, gave a 3·720% solution of the acid (XV), which had α −0·41°, [*M*] −9·6°. The resolution was therefore complete.

A benzene solution of the *l*-acid (XV) was evaporated in a desiccator to a thick syrup, which would not crystallise; it was therefore vigorously triturated with pure petrol (b. p. 40—60°), whereby it was rapidly converted into a sticky but almost solid white mass. Further confinement in a vacuum removed traces of petrol and gave the pure l-*acid* (XV) (Found: C, 62·3; H, 6·4. $C_{16}H_{21}O_3SP$ requires C, 62·1; H, 6·05%). This acid is freely soluble in most organic solvents except *cyclo*hexane and petrol, but is insoluble in water: all attempts to crystallise it failed, however.

When a solution of the acid in aqueous ammonia was evaporated at room temperature in a vacuum, the pure l-*ammonium* salt was obtained as a crisp, brittle glass that could be readily powdered (Found: N, 3·8. $C_{16}H_{21}O_3SP,NH_3$ requires N, 3·8%). A 4·770% aqueous solution of this salt gave the following rotations:

Source of light.	λ, A.	α.	[*M*].	Source of light.	λ, A.	α.	[*M*].
Li	6708	−0·50°	− 9·6°	Hg	5461	−0·60°	−11·5°
Li	6104	−0·55	−10·5	Cd	5086	−0·43	− 8·2
Na	5893	−0·56	−10·7	Hg	4358	−0·03 *	− 0·6 *
Hg	5780	−0·62	−11·9				

* High accuracy is not claimed for these values owing to the small rotation and considerable absorption of the light.

The ammonium salt can be recrystallised from a concentrated solution in benzene if the latter is saturated with ammonia to suppress dissociation: the salt is thus obtained in colourless, fibrous crystals which on heating dissociate with slow liquefaction between 40° and 80° (Found: N, 3·85%).

The mother-liquors from the preparation and first five recrystallisations of the above *d*-amine salt were united, evaporated to dryness, and the residue decomposed and extracted with a mixture of benzene and dilute sulphuric acid. The benzene solution of the free phosphine sulphide acid (XV) thus obtained was further extracted twice with the sulphuric acid to ensure total removal of the amine. The benzene was then evaporated, and the residual acid (XV) dissolved in alcohol, neutralised with alcoholic sodium hydroxide, and treated with *l*-α-phenylethylamine hydrochloride. The optically impure l-*amine* d-*acid* which separated, when once recrystallised from alcohol, had m. p. 193—200°; eight more recrystallisations from alcohol gave the optically pure salt, m. p. 209—210° (Found: C, 66·8; H, 7·0; N 3·1. $C_{16}H_{21}O_3SP,C_8H_{11}N$ requires C, 66·65; H, 6·9; N, 3·0).

This salt, decomposed as before, furnished a 3·732% benzene solution of the pure *d*-phosphine sulphide acid (XV), which had α +0·41°, [*M*] +9·6°. This solution gave the pure d-*acid* as a sticky white solid which could not be crystallised (Found: S, 9·4. $C_{16}H_{21}O_3SP$ requires S, 9·3%). The acid furnished the d-*ammonium* salt as described above (Found: N, 3·75%): a 3·142% aqueous solution of this salt had α_{5893} +0·39°, α_{5461} +0·42°; $[M]_{5893}$ +11·3°, $[M]_{5461}$ +12·2°. It was also recrystallised from benzene saturated with ammonia.

Phenyl-p-*anisylethylphosphine* was obtained by the action of the chloro-phosphine (X; 36 g.) in ether (500 c.c.) on a Grignard reagent prepared from ethyl bromide (34 c.c., 3 mols.), magnesium (13 g.), and ether (200 c.c.). The usual treatment and fractionation ultimately gave the oily ethylphosphine, b. p. 137°/0·1 mm., 210—211°/20 mm. (Found: C, 73·4; H, 7·2. $C_{15}H_{17}OP$ requires C, 73·75; H, 7·0%). This phosphine was characterised by direct union with methyl iodide in ethereal solution, giving *phenyl*-p-*anisylmethylethylphosphonium iodide* (ethyl alcohol–ether), m. p. 114—115° (Found: I, 33·0. $C_{16}H_{20}OIP$ requires I, 32·9%). This salt could not be converted into a crystalline camphor- or bromo-camphor-sulphonate.

Phenyl-p-*hydroxyphenylethylphosphine*.—A mixture of the above tertiary phosphine (27 g.) and constant-b. p. hydriodic acid (120 c.c.) was treated as previously described. The product was diluted with water, basified with sodium hydroxide, and extracted with benzene. The benzene extract, on careful fractional distillation, gave a main fraction of the hydroxy-phosphine, b. p. 160—175°/0·1 mm., 17 g. This phosphine, an exceedingly viscous liquid, was characterised as its *benzoyl* derivative, needles (alcohol), m. p. 79—80° (Found: C, 75·0; H, 5·9. $C_{21}H_{19}O_2P$ requires C, 75·5; H, 5·7%); this readily united with sulphur in benzene solution to give the p-*benzoyloxy-phosphine sulphide*, colourless crystals (alcohol), m. p. 83—84°, depressed to 68—76° by admixture with the previous compound (Found: C, 68·4; H, 5·7. $C_{21}H_{19}O_2SP$ requires C, 68·8; H, 5·2%).

Phenyl-p-(*carboxymethoxy*)*phenylethylphosphine Sulphide* (as XV).—Rhombic sulphur (2·2 g., 1 atom), when added to a solution of the above hydroxy-phosphine (16 g.) in benzene (100 c.c.), slowly dissolved with heat evolution. The solution was then boiled for 10 minutes, and the solvent removed. The residual viscous phosphine sulphide could not be crystallised, and was therefore dissolved in sodium ethoxide solution (sodium, 2 g.; alcohol, 100 c.c.), ethyl bromoacetate (16 g.) added, and the mixture refluxed for 1 hour. Water (100 c.c.) was then added, and the alcohol boiled off, the solution being meanwhile kept just alkaline by addition of 10% aqueous sodium hydroxide. Water (100 c.c.) was again added and, after cooling to 30°, the mixture was rapidly extracted with benzene to remove oily impurities; on further cooling and scratching, the sparingly soluble *sodium* salt of the above carboxymethoxy-sulphide crystallised, a second small crop being obtained by adding brine to the mother-liquor. Recrystallisation from water gave the pure, very hygroscopic sodium salt (10 g.) (Found: C, 55·3; H, 5·0. $C_{16}H_{16}O_5SPNa$ requires C, 56·1; H, 4·7%).

The sodium salt was decomposed with dilute sulphuric acid and the product extracted with benzene; evaporation of the benzene from the washed and dried extract ultimately gave the free acid, which, although analytically pure, remained for many weeks as a viscous syrup. Solidification finally occurred, and the product was then recrystallised by adding benzene to a boiling suspension in *cyclo*hexane until a clear solution was obtained; slow cooling gave colourless crystals of *phenyl*-p-(*carboxymethoxy*)*phenylethylphosphine sulphide*, m. p. 84° (Found: C, 60·4; H, 5·3. $C_{16}H_{17}O_3SP$ requires C, 60·0; H, 5·3%).

The l-*phenylethylamine* salt rapidly crystallised when solutions of the sodium salt (18·3 g.) and the amine hydrochloride (8·5 g.) in water (200 c.c. and 50 c.c.) were mixed at 40° and cooled; m. p. 206—207°, unchanged by four recrystallisations from water or by three from alcohol (Found: C, 65·3; H, 7·0; N, 3·2. $C_{16}H_{17}O_3SP,C_8H_{11}N$ requires C, 65·3; H, 6·4; N, 3·2%). The salt was too slightly soluble in cold solvents for rotation measurements. A portion of the final crop was shaken with dilute sulphuric acid and benzene, the benzene solution of the free phosphine sulphide separated, and twice extracted with dilute acid, but it was optically inactive.

The d-sec.-*butylamine* salt, similarly obtained by using an excess of amine hydrochloride, was recrystallised six times from water; m. p. 189—190° (Found: C, 61·4; H, 7·4; N, 3·5. $C_{16}H_{17}O_3SP,C_4H_{11}N$ requires C, 61·1; H, 7·2; N, 3·6%). A benzene solution of the free acid, obtained as above, was inactive. The salt was also recrystallised three times from ethyl alcohol–acetone; m. p. 190—193°; a 0·718% alcoholic solution had α + 0·38°, *M* + 52°, but again furnished the inactive acid.

The d-*aminocamphor* salt, similarly obtained from aqueous solution, separated as a viscous syrup which rapidly solidified; after four recrystallisations from alcohol, it had m. p. 166—168° (Found: C, 64·4; H, 7·4. $C_{16}H_{17}O_3SP,C_{10}H_{17}ON$ requires C, 64·1; H, 7·0; N, 2·9%). It also furnished the inactive acid.

Phenyl-p-*anisyl*-n-*propylphosphine*.—This was prepared by addition of the phosphine (X; 39 g.) in benzene (80 c.c.) to a Grignard reagent prepared from *n*-propyl bromide (29 c.c.) and magnesium (8 g.) in ether (175 c.c.). After the usual treatment, distillation of the residue gave the crude phosphine, b. p. 155—165°/0·2 mm. (23 g.), and redistillation gave the pure oily *phosphine*, b. p. 163·5°/0·3 mm. (Found: C, 74·2; H, 8·0. $C_{16}H_{19}OP$ requires C, 74·4; H, 7·4%). The phosphine in ethyl acetate combined readily with methyl iodide, giving *phenyl*-p-*anisylmethyl*-n-*propylphosphonium iodide*, colourless crystals (ethyl acetate or water), m. p. 114° (Found: I, 31·7. $C_{17}H_{22}OIP$ requires I, 31·7%), freely soluble in most organic liquids except ethyl acetate, ether, and *cyclo*hexane. It could not be converted into a crystalline camphor- or bromocamphor-sulphonate.

Phenyl-p-*anisyl*-p-*tolylphosphine*.—Addition of the phosphine (X; 34·7 g.) in ether (50 c.c.) to a Grignard reagent prepared from *p*-bromotoluene (70 g.; 3 mols.) and magnesium (9·5 g., 2·85 atoms) in ether (125 c.c.), followed by the usual procedure and fractional distillation, ultimately gave the pure *phosphine*, b. p. 176—183°/0·03 mm., 197—200°/0·1 mm.; it readily solidified and gave colourless crystals (methyl alcohol), m. p. 116—118° (Found: C, 78·1; H, 6·6. $C_{20}H_{19}OP$ requires C, 78·4; H, 6·25%). It combined readily with sulphur in carbon disulphide solution to give a *sulphide* (ethyl alcohol), m. p. 121—124° (Found: C, 71·6; H, 5·8. $C_{20}H_{19}OSP$ requires C, 71·0; H, 5·6%). It also combined with *p*-chlorophenacyl bromide (1 mol.) in warm benzene, precipitating the heavy oily *phenyl*-p-*anisyl*-p-*tolyl*-p-*chlorophenacylphosphonium bromide*; after evaporation of the solvent the bromide solidified on trituration with petrol. Recrystallisation was difficult: addition of petrol to a warm acetone solution until faintly turbid, followed by slow cooling, gave the crystalline bromide, m. p. 199° (Found: C, 62·5; H, 4·7. $C_{28}H_{25}O_2ClBrP$ requires C, 62·3; H, 4·7%). The corresponding camphor- and bromocamphor-sulphonate could not be obtained crystalline.

Phenyl-p-*bromophenyl*-p-*anisylphosphine*.—This was prepared by addition of the phosphine (II; 31 g.) in ether (100 c.c.) to a Grignard reagent prepared from *p*-bromoanisole (33 c.c.) and magnesium (6·5 g.) in ether (140 c.c.). Repeated fractionation of the final residue gave the *phosphine*, b. p. 204°/0·01 mm., which ultimately solidified; colourless crystals (methyl alcohol), m. p. 71° (Found: Br, 21·4. $C_{19}H_{16}OBrP$ requires Br, 21·5%).

Dichlorobis(*phenyl*-p-*bromophenyl*-p-*dimethylaminophenylphosphine*)*palladium* (XVI).—When cold solutions of the phosphine (III; 1 g.) in alcohol (30 c.c.) and of ammonium palladochloride (0·36 g.) in water (4 c.c.) and alcohol (8 c.c.) were mixed, the *compound* (XVI) (0·8 g.) was rapidly precipitated as a brick-red powder. It was recrystallised from benzene, toluene, diacetone alcohol, and from alcoholic ethylene dibromide: all such samples were identical, orange, microcrystalline powders, which on heating shrank at *ca.* 240°, effervesced with partial melting at 247—249°, and finally formed a semi-solid, bright red mass at 250° (Found: C, 51·7; H, 4·5. $C_{40}H_{38}N_2Cl_2Br_2P_2Pd$ requires C, 50·8; H, 4·1%).

Dichlorobis(*phenyl*-p-*bromophenylethylphosphine*)*palladium* (XVII).—When solutions of the tertiary phosphine (7 g.) in alcohol (10 c.c.) and the palladochloride (3·4 g.) in water (35 c.c.) and alcohol (70 c.c.) were shaken together for 1 hour, the immediate precipitate formed a brown gum, which when collected and triturated with hot alcohol furnished (XVII) (5 g.) as a yellow powder. When this was fractionally crystallised from *n*-propyl alcohol, *n*-butyl alcohol, ethyl carbonate, diacetone alcohol and glycol monomethyl ether, and was also fractionally extracted with boiling acetone, no indication of isomerism could be detected, the *compound* (XVII) being obtained as minute, orange needles, m. p. 172·5—174° (decomp., with shrinking at 170°) (Found: C, 43·3; H, 3·9. $C_{36}H_{28}Cl_2Br_2P_2Pd$ requires C, 43·6; H, 3·7%).

Tri-2-*pyridylphosphine*.—This was prepared similarly to (VI), phosphorus trichloride (5·6 c.c.) in benzene (100 c.c.) being added to an "entrainment" Grignard reagent prepared from ethyl bromide (1 + 10·5 c.c.), 2-bromopyridine (28·8 c.c.), and magnesium (15 g.) in ether (300 c.c.). After the initial reaction, the ether was displaced and more benzene (150 c.c.) added. Distillation of the residue gave two main fractions: (i) b. p. 90—130°/0·15 mm., 2 : 2′-dipyridyl, which rapidly solidified in the receiver; (ii) b. p. 170—230°/0·15 mm. (mainly at *ca.* 210°), a viscous, red liquid. The latter, when dissolved in an equal volume of methyl alcohol and set aside at 5° for 2 days, deposited the crystalline *phosphine* (2·25 g.), a further 0·86 g. being subsequently obtained from the mother-liquor; colourless crystals (methyl alcohol), m. p. 113—114° (Found: N, 15·8. $C_{15}H_{12}N_3P$ requires N, 15·8%). The triethylphosphine formed as a by-product in the above reaction distilled over when the benzene was removed.

Tri-2-*pyridylarsine*.—This was prepared as for the phosphine, but by using arsenic trichloride (11·8 g., 5·4 c.c.). Fraction (ii), which now had b. p. 180—210°/0·1 mm. (mainly *ca.* 200°), was a viscous gum (9 g.) which ultimately solidified. Recrystallisation from *cyclo*hexane gave the colourless *arsine*, m. p. 85° (Found: N, 14·0. $C_{15}H_{12}N_3As$ requires N, 13·6%), very soluble in alcohol and benzene.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 23rd*, 1944.]

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75. *The Triterpene Group. Part XI. The Non-Saponifiable Matter of Lactucarium Germanicum.*

By JAMES C. E. SIMPSON.

The non-saponifiable matter of Lactucarium germanicum has been examined. It is shown that the conflicting results of earlier workers are due to failure to isolate pure constituents from the complex mixture of triterpene alcohols present in the latex. Three of these alcohols have now been obtained in a state of purity, namely, taraxasterol, β-amyrin, and a new monohydric alcohol, *germanicol*, of probable formula $C_{30}H_{50}O$.

LACTUCARIUM germanicum, the dried latex of *Lactuca virosa*, contains a mixture of crystalline esters. Many attempts have been made by various workers to isolate the esters or the related alcohols in a state of purity, with conspicuous lack of success. Following the earliest memoirs of a century ago, investigations have been carried out by, amongst others, Hesse (*Annalen*, 1886, **234**, 243; 1888, **244**, 268), Kassner (*ibid.*, 1887, **238**, 220), Pomeranz and Sperling (*Monatsh.*, 1904, **25**, 785), and Bauer and Schub (*Arch. Pharm.*, 1929, **267**, 413), and Zellner and his pupils (*Monatsh.*, 1926, **47**, 681) have examined the latex of the closely related *Lactuca sativa*. Each of the authors named appears to have believed that a successful isolation of pure constituents had been accomplished, but a comparison of the published results (Tables I and II) shows this to be untrue, because, although some measure of general agreement is apparent, discrepancies in detail are abundant. The

TABLE I.

Sources and Constants of "α-Lactucerol."

Genus and species.	Alcohol (Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).				Acetate (Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%).				Benzoate (Calc. for $C_{37}H_{54}O_2$: C, 83·8; H, 10·3%).			
	M. p.	$[\alpha]_D$.	% C.	% H.	M. p.	$[\alpha]_D$.	% C.	% H.	M. p.	$[\alpha]_D$.	% C.	% H.
1	179°	+76°	82·4	11·4	210°	63°	79·1	10·7	156°	—	81·8	10·4
2	No alcohol resembling α-lactucerol obtained											
3	194	52	83·0	11·5	215	—	80·6	11·1	—	—	—	—
4	217	97	83·7	11·7	250	—	81·5	11·2	257	—	83·5	10·3
5	180	—	82·1	11·3	—	—	—	—	—	—	—	—
6	197	—	83·8	12·0	220	—	—	—	—	—	—	—
7	197	—	—	—	220	—	81·6	10·9	—	—	—	—
8	199	—	—	—	—	—	—	—	—	—	—	—
9	206	94·5	83·5	11·7	220	—	80·6	11·6	—	—	—	—
10	No data given for α-lactucerol											
11	203	78·4	84·2	11·7	—	—	—	—	257	—	83·4	10·6
12	*ca.* 179	50	—	—	210	73	80·6	11·1	—	—	—	—
13 *	224	89	84·1	11·9	239	—	82·3	11·2	255—257	—	83·7	10·3

TABLE II.

Sources and Constants of "β-Lactucerol."

Genus and species.	Alcohol (Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).				Acetate (Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%).				Benzoate (Calc. for $C_{37}H_{54}O_2$: C, 83·8; H, 10·3%).			
	M. p.	$[\alpha]_D$.	% C.	% H.	M. p.	$[\alpha]_D$.	% C.	% H.	M. p.	$[\alpha]_D$.	% C.	% H.
1	—	38°	82·5	11·6	230°	—	78·9	10·5	—	—	—	—
2	154°	—	83·4	11·3	184	50°	80·2	10·5	—	—	—	—
3	150	—	83·4	12·1	228	—	—	—	—	—	—	—
4	155	—	83·3	11·6	210	—	—	—	—	—	—	—
5	150	48·5	83·8	12·2	—	—	—	—	—	—	—	—
6	150	—	84·2	12·1	—	—	—	—	—	—	—	—
7	150	—	84·3	11·7	285·	—	—	—	—	—	—	—
8	155	—	—	—	—	—	—	—	—	—	—	—
9	152	49	83·8	12·8	282	—	82·5	11·2	—	—	—	—
10	154	—	84·3	11·5	—	—	—	—	—	—	—	—
11	165	54	84·3	12·1	—	—	—	—	260°	—	83·8	10·4
12	No data given for β-lactucerol											
13 *	178—180	51	84·0	11·8	232	—	81·9	11·7	222—224	—	83·7	10·3

1 *Lactuca virosa*; Hesse, *loc. cit.*
2 *L. virosa*; Pomeranz and Sperling, *loc. cit.*
3 *Sonchus arvensis*; Stern and Zellner, *loc. cit.*
4 *Taraxacum officinale*; Zellner and co-workers, *loc. cit.*
5 *L. sativa*; *idem, ibid.*
6 *S. asper*; *idem, ibid.*
7 *Tragopogon pratensis*; *idem, ibid.*
8 *Cichorium endivia*; *idem, ibid.*
9 *C. intybus*; *idem, ibid.*
10 *Scorzonera hispanicus*; *idem, ibid.*
11 *L. virosa*; Bauer and Schub, *loc. cit.*
12 *L. virosa*; Kassner, *loc. cit.*
13 *L. virosa*; Bauer and Brunner, *Arch. Pharm.*, 1938, **276**, 605.

TABLE III.

Sources and Constants of Taraxasterol.

Genus and species.	Alcohol, $C_{30}H_{50}O$.				Acetate, $C_{32}H_{52}O_2$.				Benzoate, $C_{37}H_{54}O_2$.			
	M. p.	$[\alpha]_D$.	% C.	% H.	M. p.	$[\alpha]_D$.	% C.	% H.	M. p.	$[\alpha]_D$.	% C.	% H.
1	221—222°	+96°	84·5	11·7	251—252°	102·5°	81·9	10·9	232°	—	83·2	10·0
2	221—222	96	84·5	11·7	251—252	100·5	82·1	11·7	242—244	107°	83·5	10·1
3	217—219	96	84·4	11·7	248—250	99	81·7	11·2	—	—	—	—
4	220—221	—	—	—	250—252	101	—	—	—	—	—	—
5	221—222	97	84·6	11·6	250—251	97	—	—	242—244	105	—	—

1 *Taraxacum officinale*; Power and Browning, *loc. cit.*
2 *Taraxacum officinale*; Burrows and Simpson, *loc. cit.*
3 *Anthemis nobilis*; Power and Browning, *loc. cit.*
4 *Anthemis nobilis*; Burrows and Simpson, *loc. cit.*
5 *Lactuca virosa*; this paper.

* The literature regarding these alcohols is further complicated by the fact that Bauer and Brunner claim to have isolated lactucadiene, $C_{30}H_{48}$, m. p. 154°, from both "α"- and "β-lactucerol." As the ketones derived from each alcohol are not identical, this claim involves a novel relationship between the two alcohols; however, in view of the work described in the present paper, Bauer and Brunner's claim should be accepted with the greatest reserve, as they have not established the homogeneity of "β-lactucerol," and its contamination with taraxasterol seems to be extremely likely. A recent publication by Hesse, Eilbracht, and Reichender, of which only the abstract (*A.*, 1942, II, 43) is available, states that "α-lactucerol" from *Calotropis* resin is identical with taraxasterol. The authors regard it as a *primary* alcohol, but state that it gives sapotalin on dehydrogenation and that treatment with acids converts it into "*iso*lactucerol." This substance may conceivably be a slightly impure specimen of ψ-taraxasterol (Burrows and Simpson, *loc. cit.*; Morice and Simpson, J., 1940, 795), particularly as Murti and Seshadri (*A.*, 1944, II, 110), working with *Calotropis gigantea*, isolated a substance named β-calotropeol. Dr. Murti's thesis has just been in the present author's hands, and, short of confirmation by mixed melting points, the identity of β-calotropeol with ψ-taraxasterol is highly probable. Our experience with ψ-taraxasterol has shown that its complete separation from taraxasterol is almost impossible, and the isomerisation recorded by Hesse *et al.* may not have been quantitative.

only facts beyond dispute are that the latex contains a mixture of high-melting dextrorotatory acetates (known variously as lactucerin and lactucon), and that on hydrolysis these yield crystalline dextrorotatory alcohols of uncertain composition, to which the names " α- and β-lactucerol " (or " -lactucol ") have been ascribed.

Despite the fact that the properties of these alcohols depend markedly on the source from which they are prepared, Zellner (*loc. cit.*; also Stern and Zellner, *ibid.*, 1925, **46**, 458) has assumed that " α- " and " β-lactucerol " are two homogeneous entities, and has sought to show that they are characteristic constituents of various species of *Compositæ* (of which *Lactuca* is one genus). In addition, he has claimed that " α-lactucerol " is identical with the triterpene alcohol taraxasterol, which has been isolated in a state of undoubted purity from two *Compositæ* species, namely, *Taraxacum officinale* (Power and Browning, J., 1912, **101**, 2411; Burrows and Simpson, J., 1938, 2042) and *Anthemis nobilis* (Power and Browning, J., 1914, **105**, 1829; Burrows and Simpson, *loc. cit.*). A comparison of Tables I, II, and III shows that, while the evidence on which Zellner's claims are based is inadequate and unconvincing (it appears to lack even the support of mixed melting point determinations), it is yet sufficiently suggestive to warrant a closer investigation of the *Compositæ* species in question.

The experiments now reported show that Lactucarium germanicum does in fact contain taraxasterol, although probably not as a major component. The non-saponifiable matter consists almost entirely of a mixture of crystalline alcohols, which, judged from their general properties, are undoubtedly of triterpenoid character. The mixture is excessively complex, and a meticulous examination of the small quantity available was not attempted. However, the presence of β-amyrin was established, and a new triterpene alcohol was isolated without much difficulty. This substance has been named *germanicol*, and appears to be present in fair quantity; it melts at 177°, has the formula $C_{30}H_{50}O$, is unsaturated to tetranitromethane, and gives a crystalline *acetate* (m. p. 274—276°) and *benzoate* (m. p. 270°).

The names lactucerin, lactucon, α- and β-lactucerol, and α- and β-lactucol must now be regarded as descriptive of mixtures. No fraction having a constant melting point similar to that of " β-lactucerol " was encountered, but a significant fact is that the published melting points of several preparations of " α-lactucerol " lie very close to the melting point (195—197°) of what was found, in the present work, to be a constant-melting mixture containing taraxasterol.

The difference between these results and those of earlier workers is believed to be due to experimental procedure and not to phyllogenetic causes. The inclusion of a stage involving adsorption on activated alumina appears to be an essential step; it has yielded good results in similar problems (*e.g.*, Burrows and Simpson, *loc. cit.*; Morice and Simpson, J., 1940, 795; 1941, 181; Barton and Jones, J., 1943, 599), and a careful re-examination of other *Compositæ* species by the chromatographic procedure would probably yield valuable and conclusive results. In addition, such work might well disclose a practicable source of taraxasterol, which is of particular interest in that its double bond is easily reducible (Burrows and Simpson, *loc. cit.*), a fact which, from analogy with lupeol and betulin, is suggestive of nuclear divergence from the amyrin type.

Experimental.

Melting points are uncorrected. Specific rotations were determined in chloroform in a 1-dm. tube. The ligroin used had b. p. 40—60°.

Preparation of Non-saponifiable Matter.—Commercial Lactucarium germanicum of British origin (110 g.) was broken into pieces the size of a pea and left under ligroin (1000 c.c.) for a fortnight with occasional shaking. The liquid was decanted, and the residue left for 10 days with more ligroin (750 c.c.). Evaporation of each extract left a solid mass (40 g. and 3 g. respectively). The total ligroin-soluble material was refluxed for 4 hours with a solution of potassium hydroxide (50 g.) in water (50 c.c.), alcohol (700 c.c.), and benzene (150 c.c.). The solution, from which a little insoluble rubber-like material (subsequently discarded) had separated, was then concentrated, 500 c.c. of solvent being recovered. The residue was diluted with water to 2·5 l. and extracted with ether. A small amount (*ca.* 0·5 g.) of a silky crystalline substance, insoluble in dilute potassium hydroxide solution, in ether, and in chloroform, separated from the ethereal phase during the extraction. The filtered ethereal extract was washed twice with water, a gel forming in the aqueous phase during this process. The aqueous gel was re-extracted with ether, and the extract added to the main ethereal solution. Acidification of the alkaline solution gave a low-melting mixture of solid acids (4 g.). Evaporation of the washed and dried neutral fraction yielded an almost white crystalline mass (33 g.), easily soluble in benzene and sparingly soluble in ligroin.

Preliminary Fractionation of Non-saponifiable Matter.—A solution of the foregoing material (33 g.) in 800 c.c. of benzene–ligroin (5 : 3) was drawn through a column (80 × 2·8 cm.) of Merck's activated alumina prepared by suspending 400 g. in 800 c.c. of benzene–ligroin (1 : 1). The column was then washed with successive portions of solvent, which were worked up separately as follows:

Fraction No.	Washing solvent.	Weight (g.).	Appearance.
1	Original filtrate	1·2	Yellow mobile oil; strong musty odour similar to that of original latex
2	Benzene–ligroin (800 c.c., 5 : 3)	16·5	Crystalline solid
3	Benzene–ligroin (800 c.c., 6 : 2)	5·3	Crystalline solid
4	Benzene–ligroin (800 c.c., 6 : 2)	2·5	Crystalline solid
5	Benzene–ligroin (800 c.c., 6 : 2)	1·3	Crystalline solid
6	Benzene (800 c.c.)	0·5	Yellow resin
7	Benzene (800 c.c.)	0·2	Yellow resin
8	Ether–benzene (800 c.c., 3 : 5)	0·5	Yellow resin
9	Ether–benzene (800 c.c., 1 : 1)	0·7	Yellow frothy mass
10	Ether (800 c.c.)	1·1	Partly crystalline
11	Ether (800 c.c.)	0·2	Yellow resin
12	Ether (1600 c.c.)	0·2	Yellow resin
13	Methanol–benzene *ad lib.*	2·0	Yellow resin
		32·2	

Isolation of Taraxasterol.—Fractions 3, 4, and 5 were separately crystallised from alcohol; each had roughly the same solubility, and the initial crop in each case melted at about 160°. After several further crystallisations the m. p. in each case rose to *ca.* 185—190°. These crops were combined (2·78 g.), and the crystallisations continued; a mixture was thus obtained which behaved as a pure substance, as it melted at 195—197° during three successive crystallisations. The final crop (0·73 g.) was acetylated (pyridine and acetic anhydride), as was also the material (1·42 g.) remaining in the mother-liquor from this and the two preceding crystallisations. The resultant acetates were separately crystallised from benzene–alcohol until the m. p., originally 215—225°, rose to 242—244°. At this point the crops were combined (0·42 g.) and crystallised from ethyl acetate; taraxasteryl acetate (0·25 g.) was thus obtained as irregular plates, m. p. 250—251°, $[\alpha]_D^{20°}$ +97° (c = 2·10), which gave no depression when mixed with an authentic specimen (m. p. 250—252°, $[\alpha]_D$ +100·5°) obtained from *taraxacum* root.

Hydrolysis of the acetate (3% benzene–alcoholic potassium hydroxide) gave taraxasterol, which separated from alcohol in soft fluffy needles, m. p. 221—222°, $[\alpha]_D^{17°}$ +97° (c = 1·65) (Found: C, 84·6; H, 11·6. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). No depression in m. p. was observed when this preparation was mixed with an authentic sample of m. p. 221—222° and $[\alpha]_D$ +96°. Benzoylation of the alcohol gave taraxasteryl benzoate, m. p. 242—244°, $[\alpha]_D^{19°}$ +105° (c = 1·85), which showed no depression when mixed with authentic material (m. p. 242—244°, $[\alpha]_D$ +107°).

Germanicyl Acetate.—Fraction 2, which was extremely soluble in alcohol, yielded 10·5 g. (A), m. p. 145—150°, after a single crystallisation from ether–aqueous alcohol. This material was acetylated (15 c.c. of pyridine, 15 c.c. of acetic anhydride) at 100°, and the mixed acetates (m. p. 210—230°), isolated by dilution with water, were repeatedly crystallised from benzene–alcohol, and finally from ethyl acetate. *Germanicyl acetate*, which was sparingly soluble in this solvent, formed long, triangular, transparent laminæ, m. p. 274—276°, $[\alpha]_D^{20°}$ +18·1° (c = 2·155), which gave a pale yellow colour with tetranitromethane in chloroform (Found: C, 82·1; H, 11·25. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). The compound was also isolated in smaller quantity from the mother-liquor of (A) after acetylation; total yield, 1·25 g.

Hydrolysis of germanicyl acetate (4% benzene–alcoholic potassium hydroxide under reflux) yielded *germanicol*, which separated from aqueous alcohol in tufts of small prismatic needles, m. p. 176—177°, $[\alpha]_D^{17°}$ +5·8° (c = 2·925) (Found: C, 84·0; H, 11·75. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%).

Germanicyl benzoate, prepared by benzoylation of the alcohol in pyridine at 100°, was very sparingly soluble in hot acetone, gave an approximately 2% solution in boiling ethyl acetate, and separated from benzene–alcohol in thin brittle plates, m. p. 269—270°, $[\alpha]_D^{19°}$ +39·0° (c = 2·26) (Found: C, 84·2; H, 10·35. $C_{37}H_{54}O_2$ requires C, 83·8; H, 10·3%).

Isolation of β-Amyrin.—The material remaining in the earlier benzene–alcohol mother-liquors, from which germanicyl acetate was obtained, was collected and fractionally crystallised from ethyl acetate. After removal of a number of fractions which apparently consisted of impure germanicyl acetate, several crops of prismatic needles were obtained which melted at *ca.* 225—230° and showed no depression when mixed with β-amyrin acetate. A specimen of the same purity was also obtained by acetylation of the material remaining in the first mother-liquors from fractions 3, 4, and 5. As further purification of this crude acetate by crystallisation seemed hopeless, it (1·4 g.) was hydrolysed with 2½% alcoholic potassium hydroxide under reflux, and the product benzoylated in pyridine solution. The mixed benzoates, crystallised once from benzene–alcohol, had m. p. 238—241° and 220—227° on admixture with β-amyrin benzoate. Continued crystallisation from ethyl acetate gave 0·5 g. of moderately pure germanicyl benzoate (this was obtained pure by further crystallisation and identified by m. p., mixed m. p., and conversion into germanicol). Extensive fractional crystallisation of the more soluble benzoates, combined with fractional digestion with ether, finally yielded 280 mg. of β-amyrin benzoate, which crystallised in the thin rhombs characteristic of this substance; it had m. p. 229—232° alone and mixed with an authentic specimen, and $[\alpha]_D^{19°}$ +93° (c = 2·92). Its identity was fully established by hydrolysis to the alcohol, m. p. 186·5—189°, $[\alpha]_D^{19°}$ +81° (c = 1·01) (a mixture with β-amyrin, m. p. 189—192°, melted at 187—190°), and this was finally converted into the acetate (characteristic rods from benzene–alcohol), which had m. p. 238—239° alone and on admixture with authentic material; $[\alpha]_D^{19°}$ +81·5° (c = 2·09). Owing to the difficulty attending its isolation, it was impossible to assess even approximately the β-amyrin content of the latex.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, February 22nd,* 1944.]

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76. *Hydroanthracenes and Hydrophenanthrenes. Part II.**

By J. W. COOK, (MISS) N. A. MCGINNIS, and STOTHERD MITCHELL.

cis-as-Octahydrophenanthrene has been isomerised by aluminium chloride to the *trans*-isomeride. Under more drastic conditions tetralin and perhydroanthracene are among the products. *trans-as*-Octahydroanthracene and a number of its derivatives have been prepared and their configurations established. Two of the five theoretically possible perhydroanthracenes have been described hitherto. A third has now been obtained. Configurations have been assigned to these three perhydroanthracenes, and evidence is given in support of the suggested configurations.

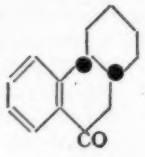
A dibenz*cyclo*octanone has been synthesised, but the small yield precluded an attempt to convert this into a derivative of *cyclo*octatetraene. 1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-Octahydro-5 : 6-benzazulene has also been synthesised, but was found to resist dehydrogenation to 5 : 6-benzazulene.

THE heterogeneity of the saturated hydrocarbons formed by dehydration of 1-β-phenylethyl*cyclo*hexanol or by isomerisation of 1-β-phenylethyl-Δ¹-*cyclo*hexene (Bogert, *Science*, **1933**, **77**, 289; Perlman, Davidson, and Bogert, *J. Org. Chem.*, **1936**, **1**, 288; Cook and Hewett, J., **1933**, 1098) was demonstrated (*a*) by fractional distillation into two fractions having different physical constants and giving different acetyl derivatives in the Friedel–Crafts reaction (van de Kamp and Mosettig, *J. Amer. Chem. Soc.*, **1936**, **58**, 1063), and (*b*) by oxidation to ketones which could be separated by fractional crystallisation of their oximes (Cook, Hewett, and Lawrence, J., **1936**, 71; Cook, Hewett, and Robinson, J., **1939**, 168; Levitz, Perlman, and Bogert, *Science*, **1939**, **90**, 114; *J. Org. Chem.*, **1941**, **6**, 105). By the latter procedure Cook *et al.* obtained (i) the oxime, m. p. 124°, of *cis*-9-keto-*as*-octahydrophenanthrene (I),† which was the major product, (ii) the oxime, m. p. 176°, of *trans*-9-keto-*as*-octahydrophenanthrene (II), and (iii) an oxime, m. p. 187°, which was assumed to be derived from

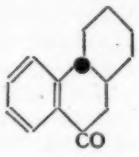
* The paper of Cook, Hewett, and Robinson (J., 1939, 168) is regarded as Part I of this series.

† Black dots in the formulæ denote hydrogen atoms above the general plane of the molecule, as in the convention proposed by Linstead (*Chem. and Ind.*, 1937, **56**, 510).

the spirocyclic ketone (III). The structures of (I) and (II) were shown by synthesis; their configurations were inferred from the physical constants of the hydrocarbons which they yielded on reduction.



(I.)



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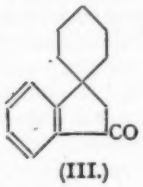

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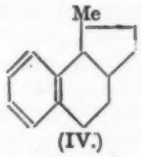


(IV.)

Bogert *et al.* likewise obtained the oxime of the *cis*-ketone (I) and the oxime, m. p. 187°, but did not succeed in isolating the oxime, m. p. 176°, of the *trans*-ketone. Instead, they isolated an oxime, m. p. 137°, which they showed by synthesis to be derived from the spirocyclic ketone (III).* Hence the ketone which yields the oxime, m. p. 187°, must have some other structure, and the elucidation of this was one of the objectives of the present work. This, however, has not been attained.

A possible, but unlikely, interpretation was that the ketone giving the oxime, m. p. 187°, was formed by oxidation of uncyclised 1-β-phenylethyl-Δ^1-*cyclo*hexene present in the hydrocarbon mixture. Oxidation experiments carried out here with this unsaturated hydrocarbon by Mr. R. B. Crane gave a ketone mixture from which the oxime in question could not be isolated. Another possibility was that octahydrophenanthrene had been partly isomerised, under conditions of its formation, to a compound of type (IV), as in the isomerisation by aluminium chloride at elevated temperatures of *cyclo*hexane to methyl*cyclo*pentane (Zelinsky and Turowa-Pollak, *Ber.*, **1932**, **65**, 1171; Nenitzescu and Cantuniari, *ibid.*, **1933**, **66**, 1097) or of decahydronaphthalene to dimethyl*bicyclo*octane (Zelinsky and Turowa-Pollak, *Ber.*, **1925**, **58**, 1292; Jones and Linstead, J., **1936**, 616). On this hypothesis, treatment of the crude *as*-octahydrophenanthrene with aluminium chloride under conditions more drastic than those used in its preparation might be expected to increase the amount of hydrocarbon yielding the desired ketone on oxidation. This would facilitate a study of the structure by degradation methods.

The crude *as*-octahydrophenanthrene was, in fact, isomerised by aluminium chloride at temperatures from 20° to 50°; oxidation of the resulting hydrocarbon mixtures gave ketone mixtures very rich in *trans*-9-keto-*as*-octahydrophenanthrene (II), which was readily isolated in the crystalline state. The original hydrocarbon mixture gave very little of this ketone. The desired oxime of m. p. 187° could not be isolated after oximation of the material from the mother-liquors of this *trans*-ketone formed by isomerisation and oxidation. The action of aluminium chloride was thus essentially a conversion of *cis-as*-octahydrophenanthrene into its *trans*-isomeride, a reaction analogous to the transformation of *cis*-decalin into *trans*-decalin by aluminium chloride at room temperature (Zelinsky and Turowa-Pollak, *Ber.*, **1932**, **65**, 1299).

At higher temperatures aluminium chloride produced more deep-seated changes. From the complex mixture formed at 125—130° were isolated tetralin, a perhydroanthracene (XIII), m. p. 89—90°, and a *hydrocarbon*, m. p. 204°, which appeared to be isomeric with this. The same products were obtained when *trans-as*-octahydroanthracene (VII) was treated with aluminium chloride under the same conditions. The formation of tetralin is evidently due to " cracking " by aluminium chloride. Possibly tetralin is an intermediate in the conversion of the tricyclic hydrocarbons into perhydroanthracene, for Schroeter (*Ber.*, **1924**, **57**, 1990), who studied the complex reactions which occur when tetralin is treated with aluminium chloride at 50—70°, isolated from the products a hydrocarbon, m. p. 93°, which he suggested was one of the possible stereoisomeric perhydroanthracenes.

Mikhlina (*Uchenuie Zapinski*, **1934**, **3**, 209; *Chem. Abstr.*, **1936**, **30**, 8192) obtained perhydroanthracene, m. p. 90°, as one of the products of cracking with aluminium chloride of *s*-octahydroanthracene, and suggested a mechanism involving primary formation of tetralin and butadiene.

The hydrocarbon, m. p. 90°, which we obtained from *as*-octahydroanthracene and *as*-octahydrophenanthrene by treatment with aluminium chloride was identical with a specimen of one of the perhydroanthracenes obtained by catalytic hydrogenation of both *s*- and *as*-octahydroanthracenes (see below). It was not dehydrogenated by heating with palladium-black at 300° or selenium at 335°, in evacuated sealed tubes. The above-mentioned hydrocarbon, m. p. 204°, was likewise unaffected by these dehydrogenating agents under the same conditions. Our failure to dehydrogenate the perhydroanthracene is at variance with the results of Koller and Russ (*Monatsh.*, **1937**, **70**, 54), who obtained anthracene when perhydroanthracene, m. p. 88°, was heated with selenium at 260—290° for 4 days in an evacuated sealed tube.

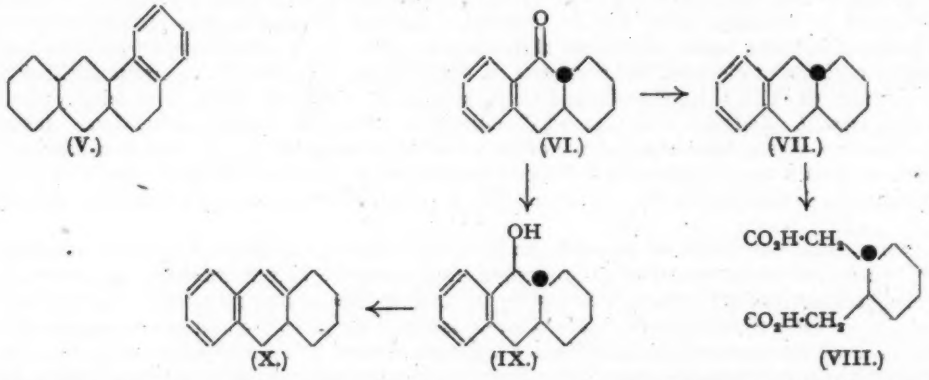
This sealed tube method of dehydrogenation, although convenient for small-scale work, seems less effective than the use of open vessels, for a dodecahydro-1 : 2-benzanthracene (V), when heated with selenium at 320—330° for 24 hours in an evacuated sealed tube, gave 5 : 6 : 7 : 8-tetrahydro-1 : 2-benzanthracene and not the

* Failure to isolate the oxime of m. p. 176° led Bogert to make the astonishing suggestion that the oxime of m. p. 187° was possibly derived from *trans*-keto-*as*-octahydrophenanthrene. This view ignored the synthesis of the *trans*-ketone giving the oxime of m. p. 176°, and also the depression of m. p. of this oxime when mixed with the oxime of m. p. 187° (J., 1936, 78). Further syntheses of the *trans*-ketone (II) have been recorded by Blumenfeld (*Ber.*, **1941**, **74**, 524) and by Linstead, Whetstone, and Levine (*J. Amer. Chem. Soc.*, **1942**, **64**, 2014).

fully aromatic 1 : 2-benzanthracene which is formed when the dehydrogenation is carried out in an open flask (Cook and Hewett, J., 1934, 375).

The configurations assigned by Cook, Hewett, and Robinson (*loc. cit.*) to the *as*-octahydrophenanthrenes were based on comparisons of their physical constants, and on the higher m. p.'s of the *trans*-ketone and its oxime. Attempts to verify the configuration of the relatively accessible *cis*-ketone (I) by degradation to *cis*-hexahydrohomophthalic acid had been unsuccessful. Hence we prepared a quantity of the *trans*-ketone (II) by our new method, with the object of degrading this to the easily crystallisable *trans*-hexahydrohomophthalic acid. This project was rendered unnecessary by the appearance of a paper by Linstead, Davis, and Whetstone (*J. Amer. Chem. Soc.*, 1942, **64**, 2009), who gave a rigid chemical proof of the configurations which we had assigned to the ketones (I) and (II). Another objective of our work was the preparation of stereochemically homogeneous perhydrophenanthrenes of known configuration, and experiments to this end are in progress with the *trans*-ketone (II).

A study of the stereochemical relationships of hydroanthracenes has also been commenced. Cook, Hewett, and Lawrence (*loc. cit.*) described a synthesis of the two stereoisomeric 9-keto-*as*-octahydroanthracenes, and suggested the *trans*-configuration (VI) for the readily available higher-melting isomeride (m. p. 109°). Proof of this has now been obtained. By Clemmensen reduction the ketone was converted into trans-as-***octahydroanthracene*** (VII). Sulphonation, followed by fusion with potash, converted this hydrocarbon into a ***hydroxy***-derivative, which was oxidised by alkaline permanganate to *trans-cyclo*hexane-1 : 2-diacetic acid (VIII).



Catalytic hydrogenation of *trans*-9-keto-*as*-octahydroanthracene over Adams's platinum catalyst gave a mixture from which were isolated *trans-as*-octahydroanthracene (VII) and its 9-*hydroxy*-derivative (IX), in which the configuration of the hydroxyl group is unknown. Dehydration of the carbinol gave ***hexahydroanthracene*** (probably X), from which it was hoped to obtain *cis-as*-octahydroanthracene by catalytic hydrogenation. Hydrogenation rapidly took place over a platinum catalyst, but the product was mostly liquid and the isolation of a pure stereoisomeride was not feasible.

Two perhydroanthracenes (tetradecahydroanthracenes) have been described in the literature. One of these, obtained by hydrogenation of anthracene or *s*-octahydroanthracene (XVI) over nickel catalysts at high temperatures, or by reduction with hydriodic acid and phosphorus, has m. p. 89—90° (figures varying between 88° and 93° have been given) (Lucas, *Ber.*, 1888, **21**, 2510; Godchot, *Compt. rend.*, 1907, **141**, 1028; Ipatiew, Jakowlew, and Rakitin, *Ber.*, 1908, **41**, 996; Fries and Schilling, *Ber.*, 1932, **65**, 1494). The other has m. p. 61° (Fries and Schilling, *loc. cit.*; Kagehira, *Bull. Chem. Soc. Japan*, 1931, **6**, 241; Brown, Durand, and Marvel, *J. Amer. Chem. Soc.*, 1936, **58**, 1594), and is formed by hydrogenation at the ordinary temperature over Adams's catalyst. However, Kagehira's product was isolated from a mixture formed by hydrogenation under pressure with nickel at 200°. The formation of this isomeride under such conditions is anomalous, but it is significant that Kagehira's hydrogenation of naphthalene under the same conditions gave a mixture of decalins which contained 90% of the *cis*-isomeride. The perhydroanthracene obtained by Prokopetz and Khadzhinov (*Khim. Tverdogo Topliva*, 1935, **6**, 347), using a molybdenum sulphide catalyst, was apparently a liquid mixture of isomerides. Hitherto, no attempt has been made to determine the configurations of the solid perhydroanthracenes, although du Feu, McQuillin, and Robinson (J., 1937, 53) have described a keto-dodecahydroanthracene (XVII), the configuration of which is partly known from its method of synthesis.

If we assume the absence of isomerism based on different multiplanar forms of the *cyclo*hexane ring (this assumption seems justified by a very large body of evidence), then there are five possible optically inactive forms of perhydroanthracene. In two of these (XI and XII) the rings are locked, in pairs, by *cis*-valency bonds; in two others (XIII and XIV) there is *trans*-locking of the rings; and in the fifth (XV), one ring fusion takes place by *cis*-valencies and the other by *trans*-valencies. We have prepared the two known perhydroanthracenes and also a third stereoisomeride, and have studied their inter-relationships and their physical constants.

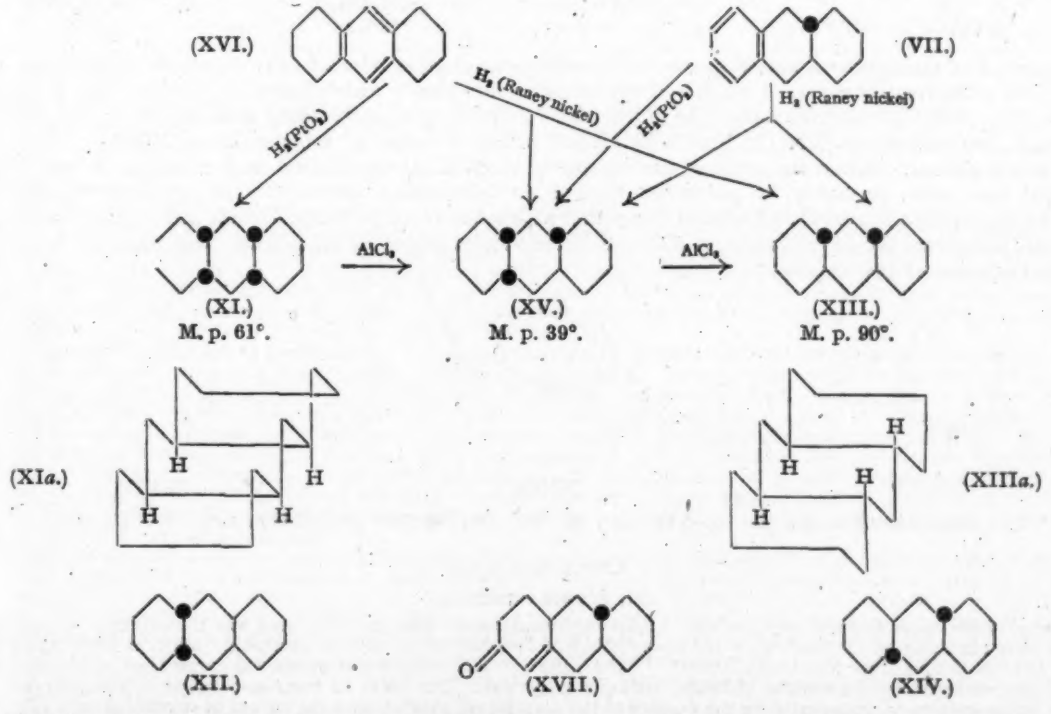
Hydrogenation over platinum catalysts in acetic acid solution usually leads almost exclusively to *cis*-compounds, and in accordance with the considerations advanced by Linstead, Doering, Davis, Levine, and

Whetstone (*J. Amer. Chem. Soc.*, **1942**, **64**, 1985) we suggest that the perhydroanthracene, m. p. 61°, is formed by addition of all the hydrogen atoms to the same side of the plane of the molecule of *s*-octahydroanthracene, and has the completely *cis*-configuration (formula XI). A space model of this configuration shows a flat molecule in which all the carbon atoms lie in two parallel planes, which are close to one another. The model shows three strainless "boat" forms of the *cyclo*hexane ring, fused as in (XI*a*). The isomeride, of m. p. 90°, formed by high-temperature hydrogenation and also by the action of aluminium chloride on tetralin, *as*-octahydroanthracene and *as*-octahydrophenanthrene, is undoubtedly one in which there are *trans*-linkages of the rings, and from considerations of molecular symmetry we suggest that the configuration is that represented by (XIII), although (XIV) is not excluded. Models show that (XIII), but not (XIV), corresponds with a flat molecule, with three strainless "chair" forms of the *cyclo*hexane ring, as in (XIII*a*).

Hydrogenation of *trans-as*-octahydroanthracene (VII) with platinum in acetic acid gave the new *perhydroanthracene*, m. p. 39°, and on Linstead's theory of one-sided addition of hydrogen this must have the configuration (XV). Fries and Schilling (*loc. cit.*) obtained the perhydride, m. p. 93°, by hydrogenation of anthracene in *cyclo*hexane solution with a nickel catalyst at 240°. They also claimed a 90% yield of the same product in the rapid hydrogenation of anthracene without a solvent at 90—110°. Using Raney nickel, we isolated only a 25% yield of this perhydride, m. p. 89—90°, when *s*-octahydroanthracene (XVI) was hydrogenated in *cyclo*hexane solution at 200°. From the more soluble products we also isolated, in 20% yield, the new perhydroanthracene (XV). Raney nickel is a very active catalyst, and it may well be that much of the hydrogenation took place at lower temperatures than that finally attained. Such conditions would favour *cis*-addition of hydrogen. The formation of these same two perhydrides by hydrogenation of *trans-as*-octahydroanthracene (VII) with Raney nickel demonstrates at least one *trans*-locking of rings in each of them. Waterman and his collaborators (*Rec. Trav. chim.*, **1934**, **53**, 821; **1939**, **58**, 83) have obtained evidence that *cis* ⟶ *trans* changes can be brought about in fully hydrogenated naphthalene and anthracene by prolonged heating under pressure with nickel and hydrogen at 260—300°, but it is very unlikely that such changes would occur under the milder conditions used in our hydrogenation experiments with Raney nickel.

When the perhydroanthracene (XI), m. p. 61°, was heated with aluminium chloride at 100° for 7 hours, it was transformed into a mobile liquid which had not crystallised after several months. If, however, the reaction was carried out at room temperature in hexane solution, there was obtained a solid mixture from which the perhydride (XV) was isolated. The latter compound was further isomerised by aluminium chloride in hexane solution, and there was isolated, in small yield, the perhydride of m. p. 90° (XIII).

These relationships are illustrated by the following scheme :



The following table of physical constants of the three perhydroanthracenes gives values which are in harmony with the proposed configurations. The compound with a complete *cis*-configuration (XI) has the highest b. p., density and refractive index, but the smallest molecular refraction; the compound which is mostly *trans* (XIII or XIV) has the lowest b. p., density and refractive index, and the largest molecular refraction.

	B. p. at 743·5 mm.	$n_D^{100°}$.‡	$d_4^{100°}$.	$[R_L]_D$.
Perhydroanthracene, m. p. 62°	282—283°	1·4810	0·9021	60·64
* ,, m. p. 32°	274—275	1·4700	0·8788	61·02
† ,, m. p. 90°	272—273	1·4637	0·8647	61·30

* The purified specimen, m. p. 39—40°, was not available in sufficient quantity for physical measurements, so the values given for this isomeride are approximate.

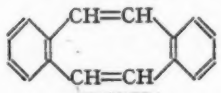
† Waterman, Leendertse, and Cranedonk (*Rec. Trav. chim.*, 1939, **58**, 83) give $n_D^{25°}$ 1·4640 and $d_4^{25°}$ 0·8729 for the perhydride, m. p. 88—89°.

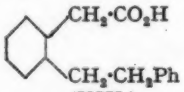
‡ For determining the refractive indices at 100° we used a spectrometer and a hollow brass prism with two glass windows cemented in position. The prism was inserted in an electrically heated steel cylinder, in the side of which holes were drilled at the appropriate angles to permit the passage of the light (from a sodium lamp). After the molten substance had been introduced, the apparatus was heated to 105°, and the readings of the angle of minimum deviation (for λ = 5893 A.) were taken at this and intermediate temperatures as it cooled to 95°. The prism angle was next measured, and the refractive index calculated for each temperature. Its value at 100° was then obtained graphically.

Dehydrogenation experiments also gave results which are consistent with the configurations suggested for the perhydroanthracenes melting at 61° and 90°. The latter (*trans-trans*) isomeride was completely resistant to selenium dehydrogenation under conditions which led to the formation of anthracene in the case of the former (*cis-cis*) isomeride.

Concurrently with the above studies, which are being continued, preliminary experiments have been carried out in connexion with two other projects:

(i) Interest in *cyclo*octatetraene has been revived by the suggestion of Hurd and Drake (*J. Amer. Chem. Soc.*, **1939, 61**, 1943) that the hydrocarbon formerly believed to be this was styrene, and several attempts to prepare the true *cyclo*octatetraene or one of its derivatives have been recorded. Tetraben*zcyclo*octatetraene has been described recently (Rapson, Shuttleworth, and van Niekerk, J., **1943**, 326). As a stage in a possible synthesis of a diben*zcyclo*octatetraene (**XVIII**) we have condensed 2-β-phenylethyl*cyclo*hexanone with ethyl bromoacetate and zinc. Dehydration of the resulting hydroxy-ester, followed by hydrogenation and hydrolysis, gave 2-β-phenylethyl*cyclo*hexylacetic acid (**XIX**) (characterised as its p-*phenylphenacyl* ester). Attempts to cyclise the crude acid gave the desired ketone (**XX**) in very unsatisfactory yield, and also a *lactone* (**XXI**) which was evidently formed by isomerisation of the unsaturated acid which had resisted hydrogenation.


(XVIII.)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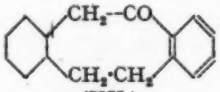
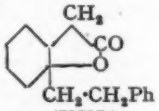
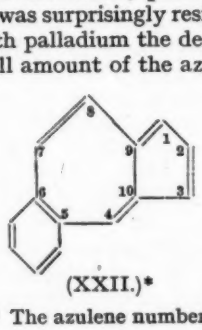
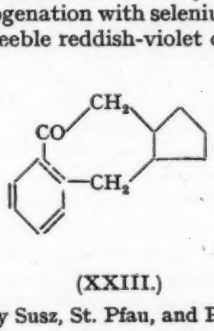
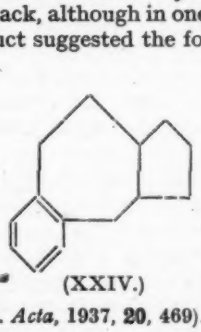

(XX.)


(XXI.)

(ii) Azulenes, containing a closed system of 5 conjugated double bonds in the *bicyclo*[0 : 3 : 5]decane ring system, are often readily obtained by dehydrogenation of less highly unsaturated compounds, and a detailed study of their chemical behaviour would be of interest. 2-Benzyl*cyclo*pentylacetic acid was converted, through its chloride, into the *ketone* (**XXIII**), from which it was hoped to obtain 5 : 6-benzazulene (**XXII**). This could not be accomplished. When the *carbinol* corresponding to (**XXIII**) was heated with selenium, it was largely converted into resin, probably by polymerisation of its dehydration product. The saturated *hydrocarbon* (**XXIV**) was surprisingly resistant to dehydrogenation with selenium or palladium-black, although in one experiment with palladium the development of a feeble reddish-violet colour in the product suggested the formation of a small amount of the azulene.


(XXII.)*


(XXIII.)


(XXIV.)

* The azulene numbering is that used by Susz, St. Pfau, and Plattner (*Helv. Chim. Acta*, **1937, 20**, 469).

Experimental.

(M. p.'s are corrected.)

Action of Aluminium Chloride on Crude as-*Octahydrophenanthrene.*—The material used was the mixture of saturated hydrocarbons obtained by cyclisation of 1-β-phenylethyl-Δ^1-*cyclo*hexene in carbon disulphide solution with aluminium chloride at room temperature (Cook and Hewett, J., **1933**, 1098). A series of experiments was carried out on the isomerisation of this material by aluminium chloride, without a solvent. The yield of *trans-as*-octahydrophenanthrene was variable, being influenced apparently by the quality of the aluminium chloride and the extent of stirring as well as by the temperature. In all cases, after oxidation and distillation, the ketonic fraction readily crystallised. This had never been observed in the many oxidations previously carried out on material which had not been submitted to the action of aluminium chloride in the absence of solvent. The following are accounts of four of the experiments:

(*a*) A mixture of crude *as*-octahydrophenanthrene (27 g.) and aluminium chloride (9 g.) was heated at 50—70°, for 15 hours, without stirring. The product, after cooling, was poured on ice and hydrochloric acid. When decomposition

of the black viscous mass was complete, the mixture was distilled in steam, and the steam-volatile oil was extracted with ether. The oil (16·5 g.) recovered from the extract was dissolved in purified acetic acid (160 c.c.) and treated slowly with a solution of chromic acid (18·3 g.) in 80% acetic acid (36 c.c.). After being kept at room temperature for 6 days, the green solution was poured into water (1·5 l.), extracted with ether, and the extract washed with sodium carbonate solution, dried, and distilled at 0·2 mm. The first fraction, b. p. 110°, was mostly hydrocarbon; the higher fraction (5·7 g.), b. p. 110—140°, slowly solidified. Crystallisation from alcohol gave *trans*-9-keto-*as*-octahydrophenanthrene (II), m. p. 95—96°, which formed an oxime, m. p. 176—177° (Cook, Hewett, and Lawrence, *loc. cit.*). The m. p. of the oxime was depressed to 147—156° by admixture with the oxime, m. p. 187°, of undetermined constitution.

(*b*) The crude *as*-octahydrophenanthrene (10 g.) was kept at room temperature for 26 hours with aluminium chloride (3·4 g.). During the first 7 hours and the last 4 hours the mixture was stirred. The product was worked up as described under (*a*) and gave, after oxidation, 1·5 g. of the *trans*-ketone (II).

(*c*) A mixture of crude *as*-octahydrophenanthrene (75 g.) and aluminium chloride (25 g.) was stirred at 60—70° for 14 hours. Much more extensive change took place than in experiment (*a*). The steam-volatile oil subsequently obtained had an odour of tetralin (see *d*, below); the less volatile portions solidified partly in the receiver. This material, triturated with a little ether, gave a solid which, after crystallisation from benzene, had m. p. 201° and was identical with the hydrocarbon obtained as described under (*d*). The total steam-volatile product amounted to only 13·5 g., and this gave very little crystalline ketone.

(*d*) A mixture of crude *as*-octahydrophenanthrene (25 g.) and aluminium chloride (8 g.) was heated at 125—130° for 24 hours. The cooled mass was decomposed with dilute hydrochloric acid, with addition of a little carbon disulphide. The product was then distilled in steam. The last portions of the steam distillate passed over very slowly and partly solidified. A solution of this fraction in hot alcohol deposited a white solid (0·25 g.), which crystallised from benzene in colourless leaflets, m. p. 203—204° (Found: C, 87·3, 87·4; H, 12·75, 12·7. $C_{19}H_{34}$ requires C, 87·4; H, 12·6%). This *hydrocarbon* (1 part) was recovered unchanged after heating in an evacuated sealed tube with palladium-black (0·5 part) at 300° for 4½ hours or with selenium (2·5 parts) at 310—325° for 24 hours. The alcoholic liquors from which this compound had been isolated were combined with the remainder of the steam-volatile products, and the whole was distilled at 15 mm. The first fraction (3 g.), b. p. to 120°, was redistilled at atmospheric pressure; it boiled mostly at 205—210°, had a strong odour of tetralin, and was dehydrogenated to naphthalene by refluxing with sulphur. The second fraction (1·5 g.), b. p. 120—150°/15 mm., and the third fraction (3 g.), b. p. 150—170°/15 mm., both crystallised in part, and the solid was isolated by cooling solutions of the distillates in hot alcohol. Both fractions gave perhydroanthracene, in colourless leaflets, m. p. 89—90° (from methyl alcohol) (Found: C, 87·35; H, 12·65. Calc. for $C_{14}H_{24}$: C, 87·4; H, 12·6%). The m. p. was not depressed by the perhydroanthracene, m. p. 89—90°, obtained by hydrogenation of *s*-octahydroanthracene. This perhydride was recovered unchanged after attempted dehydrogenation with palladium-black and selenium, under the conditions described above for the hydrocarbon of m. p. 204°. Further quantities of the latter hydrocarbon were obtained from the residue in the flask from the vacuum distillation, and also (0·3 g.) from a distillation at 1 mm. of the portion of the reaction product which did not distil in steam. This hydrocarbon, m. p. 204°, sublimed at 120°/0·1 mm.

Dehydrogenation of Dodecahydro-1 : 2-*benzanthracene* (V).—A mixture of the hydrocarbon (100 mg.), m. p. 71°, and selenium (200 mg.) was heated at 320—340° for 24 hours in an evacuated sealed tube. An alcoholic extract of the product gave, with picric acid, orange needles, m. p. 155°, consisting of the picrate of 5 : 6 : 7 : 8-tetrahydro-1 : 2-benzanthracene (Cook and Hewett, J., 1934, 375). This was the main product.

trans-as-*Octahydroanthracene and its Derivatives.*—*trans*-Hexahydroanthrone (VI) was obtained by addition of *trans*-2-benzylhexahydrobenzoic acid (108 g.) to concentrated sulphuric acid (500 c.c.). The solid dissolved rapidly, and the clear solution was poured into ice-water. The precipitate was collected and crystallised from alcohol, giving *trans*-hexahydroanthrone (70 g.), m. p. 109—110° (Cook, Hewett, and Lawrence, J., 1936, 79). Nitration of this ketone (1 part) by addition of potassium nitrate (1 mol.) to a well-cooled solution of the ketone in concentrated sulphuric acid (5 parts) gave a *nitro-ketone*, which crystallised from alcohol in colourless leaflets, m. p. 130·5—131·5° (Found: C, 68·6; H, 6·0. $C_{14}H_{15}O_3N$ requires C, 68·5; H, 5·7%).* By hydrogenation in acetone solution over palladium-black this nitro-ketone was reduced to the corresponding *amino-ketone*, which formed colourless needles (from benzene), m. p. 165—166° (Found: C, 78·2; H, 8·1. $C_{14}H_{17}ON$ requires C, 78·0; H, 8·0%).

For reduction to the hydrocarbon, *trans*-hexahydroanthrone (VI) (40 g.) was suspended in concentrated hydrochloric acid (140 c.c.), water (60 c.c.), and toluene (80 c.c.), and the whole boiled under reflux for 36 hours with amalgamated zinc (80 g.). The resulting mixture was distilled in steam. After removal of the toluene the trans-as-*octahydroanthracene* (VII) distilled slowly in steam. It crystallised from alcohol in colourless prisms (30 g.), m. p. 63—64° (Found: C, 90·5; H, 9·5. $C_{14}H_{18}$ requires C, 90·3; H, 9·7%). The residue non-volatile in steam was a white solid which crystallised from benzene in colourless needles, m. p. 245—250°. This was presumably a *hexadecahydro*-9 : 9′-*dianthryl* (Found: C, 91·2; H, 9·1. $C_{28}H_{34}$ requires C, 90·75; H, 9·25%).

9-*Hydroxy*-trans-as-*octahydroanthracene* (IX).—A solution of *trans*-hexahydroanthrone (10 g.) in acetic acid (250 c.c.) was shaken with hydrogen and Adams's platinum oxide catalyst (0·3 g.). The absorption of hydrogen was rapid, and after 50 minutes corresponded with addition of 1 molecule. Hydrogenation was, however, continued for a further hour, by which time about 30% more hydrogen had been absorbed. After filtration from catalyst the solution was freed from solvent by evaporation on the water-bath, under reduced pressure. The residual liquid was dissolved in light petroleum, and the solution strongly cooled. The crystals which separated (5·5 g.) consisted of 9-*hydroxy*-trans-as-*octahydroanthracene* (IX), which crystallised from methyl alcohol in colourless leaflets, m. p. 136° (Found: C, 82·8; H, 8·9. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%). The material from the petroleum liquors was distilled at 11 mm., and gave a distillate which largely crystallised. The crystals were drained on a tile and recrystallised from methyl alcohol, pure *trans-as*-octahydroanthracene being obtained.

Hexahydroanthracene (X).—A mixture of the aforesaid carbinol (4·5 g.) and powdered potassium hydrogen sulphate (9 g.) was heated in a flask immersed in an oil-bath kept at 160—170°, the pressure being maintained at 11 mm. The solid distillate, recrystallised from methyl alcohol, formed colourless crystals (3·3 g.), m. p. 63—66° (Found: C, 91·0; H, 9·2. $C_{14}H_{16}$ requires C, 91·2; H, 8·8%). The m. p. of this *hexahydroanthracene* was not depressed by admixture with octahydroanthracene, but, unlike the latter, the hexahydro-compound gave an orange colour with alcoholic picric acid. In an attempt to prepare *cis-as*-octahydroanthracene this hexahydroanthracene (3 g.) was hydrogenated in acetic acid solution with platinum-black. The theoretical amount of hydrogen was absorbed in 3 hours, but a homogeneous product could not be isolated.

Sulphonation of trans-as-*Octahydroanthracene.*—The hydrocarbon (VII) (3 g.) was added to concentrated sulphuric acid (10 c.c.), and the mixture was slowly heated to 70°, with continuous stirring. After the hydrocarbon had melted solution was complete in 5 minutes; the yellow solution was then cooled and treated with water (20 c.c.). After cooling to 0° the solid which had separated was collected, dissolved in warm water, and the solution made slightly alkaline with

* The preparation of this and the two following compounds was carried out by Dr. R. W. Lapsley.

sodium hydroxide. The *sodium sulphonate* (4·5 g.) crystallised on cooling as glistening white plates which crumbled to a powder when dried. It was recrystallised from water and dried in a vacuum desiccator over phosphoric oxide (Found: Na, 7·2. $C_{14}H_{17}O_3SNa,2H_2O$ requires Na, 7·1%).

ar-*Hydroxy*-trans-as-*octahydroanthracene* was obtained by addition of this sodium sulphonate (4 g.) to stirred fused potassium hydroxide (20 g.) at 230—240°. The temperature was then raised to 280° and maintained there for 1½ hours. The cooled mass was extracted with water, the extract acidified, and the phenol extracted with ether. The crude phenol, obtained from the ethereal solution, was distilled from an air-bath at 120°/0·1 mm. and then crystallised from hexane (yield, 2 g.). This *phenol*, which was mostly insoluble in alkali, formed small colourless crystals, m. p. 104° (Found: C, 83·25; H, 8·85. $C_{14}H_{18}O$ requires C, 83·1; H, 9·0%).

For oxidation, the phenol (1 g.) was added to a solution of potassium permanganate (6·3 g.) in water (125 c.c.) and 6N-potassium hydroxide (10 c.c.). The suspension was kept, with occasional shaking, for 2 days, by which time the whole of the permanganate had been reduced. The filtered solution was acidified and extracted with ether. The extract was dried with sodium sulphate and evaporated. The residual gum partly crystallised on standing, and the crystals were drained and recrystallised twice from water. The resulting colourless crystals had m. p. 166—167°, not depressed by a specimen of *trans-cyclo*hexane-1 : 2-diacetic acid (VIII) prepared by oxidation of *trans*-β-decalol, m. p. 75° (Hückel, *Annalen*, 1925, **441**, 20). There was a considerable depression of the m. p. on admixture with a specimen of *cis-cyclo*hexane-1 : 2-diacetic acid prepared by oxidation of *cis*-β-decalone.

Action of Aluminium Chloride on trans-as-*Octahydroanthracene*.—A mixture of the hydrocarbon (10 g.) and powdered anhydrous aluminium chloride (3·5 g.) was heated in an oil-bath at 130° for 30 hours. The product, which had a strong odour of tetralin, was treated with dilute hydrochloric acid, a little carbon disulphide being added to facilitate decomposition of the aluminium chloride complex. The black tarry mass was distilled in steam. The latter portions of the steam distillate solidified, and crystallisation from alcohol and then benzene gave the hydrocarbon, m. p. 202°, which had been obtained by similar treatment of crude *as*-octahydrophenanthrene. This was the only pure product isolated.

Hydrogenation of trans-as-*Octahydroanthracene* (VII).—(a) *With platinum.* A solution of the hydrocarbon (5 g.) in acetic acid (250 c.c.) was shaken with hydrogen and platinum oxide (0·25 g.) until absorption ceased. The uptake of hydrogen corresponded with addition of 3 molecules of hydrogen. Most of the acetic acid was distilled, the last traces being removed from an ethereal solution of the residue by washing with alkali. The oil which remained after evaporation of the ether crystallised when cooled, and was recrystallised from methyl alcohol, giving 3 g. of material, m. p. 32—35°. After several recrystallisations from methyl alcohol this *perhydroanthracene* (XV) formed colourless needles, m. p. 39—40° (Found: C, 87·5; H, 12·55. $C_{14}H_{24}$ requires C, 87·4; H, 12·6%).

(b) *With Raney nickel.* A solution of *trans-as*-octahydroanthracene (5 g.) in *cyclo*hexane (35 c.c.) was heated in an autoclave, with stirring, with Raney nickel (2 g.) and hydrogen. The temperature was raised to 200° (during 2½ hours) and maintained at this point for 1½ hours. The maximum pressure was 150 atms. The product was freed from solvent and recrystallised from methyl alcohol, giving 2 g. of perhydroanthracene, m. p. 89—90°, not depressed by a specimen similarly prepared from *s*-octahydroanthracene (below). The most soluble fractions from the mother-liquors crystallised with difficulty; recrystallisation from methyl alcohol gave small plates (0·2 g.), m. p. 32—34°, alone or mixed with the product obtained as described under (a).

Hydrogenation of s-*Octahydroanthracene* (XVI).—(*a*) Hydrogenation with platinum oxide in acetic acid, as described by Fries and Schilling (*Ber.*, 1932, **65**, 1499), gave in satisfactory yield large elongated plates, m. p. 61·5—63°, in conformity with the results of the German workers. This perhydroanthracene is regarded as having the completely *cis*-configuration (XI).

(*b*) A stirred mixture of *s*-octahydroanthracene (100 g.), *cyclo*hexane (250 c.c.), and Raney nickel (25 g.) was heated slowly to 200° with hydrogen under pressure. The pressure attained was 155 atms. The temperature was maintained at 200° until the pressure was constant at 115 atms. The product obtained by removal of solvent from the filtered solution was recrystallised from methyl alcohol, and gave the sparingly soluble perhydroanthracene (25 g.), m. p. 89—90°, for which we suggest the configuration (XIII). The liquors were freed from solvent and gave an oil, which slowly crystallised in part at room temperature. The crystals were collected and drained, and recrystallised from methyl alcohol. The crystals thus obtained (20 g.) had m. p. 32—34°, not depressed by the perhydroanthracene formed by hydrogenation of *trans-as*-octahydroanthracene over a platinum catalyst.

Isomerisation of Perhydroanthracenes with Aluminium Chloride.—(*a*) Powdered anhydrous aluminium chloride (2 g.) was added to a solution of perhydroanthracene (2 g.), m. p. 61°, in hexane (5 c.c.), and the suspension was kept at room temperature for 7 days, with occasional shaking. The filtered solution was washed and freed from solvent, and the residue crystallised from methyl alcohol. The colourless plates (1·3 g.) had m. p. 33—35°, not appreciably changed by further crystallisation. The m. p. was not depressed by admixture with the perhydroanthracene formed by hydrogenation of *trans-as*-octahydroanthracene with Adams's catalyst. Crystallisation from methyl alcohol of a mixture of equal parts of the isomerides melting at 61° and 90° gave material of m. p. 40—60°.

(*b*) Anhydrous aluminium chloride (2 g.) was added to a solution of perhydroanthracene (2 g.), m. p. 34°, in hexane (5 c.c.), and the suspension kept at room temperature for 4 days with occasional shaking. Crystallisation of the product from methyl alcohol gave, in addition to unchanged material, a less soluble fraction (0·5 g.), m. p. 40—65°, which, after further crystallisation, had m. p. 89—90° (0·1 g.), and was identical with the perhydroanthracene of like m. p.

Action of Selenium on Perhydroanthracenes.—(*a*) A mixture of perhydroanthracene (1 g.), m. p. 89°, and selenium (1 g.) was heated in a metal bath at 305—315° for 30 hours. The hydrocarbon boiled briskly. The product was extracted with ether and recrystallised from methyl alcohol. It had m. p. 88—90°, and was completely unchanged perhydroanthracene.

(*b*) A similar experiment was carried out simultaneously, in the same bath, with a mixture of perhydroanthracene (0·5 g.), m. p. 61°, and selenium (0·5 g.). The crude brown product, crystallised from methyl alcohol, had m. p. 170—205°, and after sublimation in a vacuum, followed by crystallisation from benzene–alcohol, the m. p. was 214—216°, and was not depressed by pure anthracene.

Ethyl 2-β-*Phenylethyl*cyclo*hexanol*-1-*acetate*.—A solution of 2-β-phenylethyl*cyclo*hexanone (Kon, J., 1933, 1083) (14·2 g.) in dry benzene (30 c.c.) was added dropwise to a suspension of zinc turnings (5·7 g.) and ethyl bromoacetate (14 g.) in dry benzene (30 c.c.). The vigorous reaction which set in on warming was completed by boiling for 2 hours. The ice-cooled product was treated with dilute sulphuric acid (20 c.c. of concentrated acid were diluted). The benzene solution was then washed with dilute sulphuric acid, sodium carbonate solution, and water, dried over sodium sulphate, and distilled. The resulting colourless liquid (12 g.) had b. p. 168—171°/1 mm.

This hydroxy-ester was dehydrated by heating for an hour with potassium hydrogen sulphate (1·5 parts), and the unsaturated ester was hydrogenated in acetic acid solution, over palladium-black. Hydrolysis of the hydrogenated ester with boiling alcoholic alkali gave the crude 2-β-phenylethyl*cyclo*hexylacetic acid (XIX) as a viscous oil, b. p. 190—200°/1 mm. Its p-*phenylphenacyl* ester crystallised from alcohol in rosettes of colourless needles, m. p. 75—77° (Found: C, 81·5; H, 7·1. $C_{36}H_{38}O_3$ requires C, 81·8; H, 7·3%).

Cyclisation of 2-β-*Phenylethyl*cyclo*hexylacetic Acid* (XIX).—(*a*) Phosphorus pentachloride (3·5 g.) was added to a

solution of the acid (3·5 g.) in dry benzene (30 c.c.) and the suspension was kept at room temperature with occasional shaking until a clear solution was formed (2 hours). The benzene and phosphorus oxychloride were removed by heating on the water-bath under diminished pressure, and a solution of the residual acid chloride in nitrobenzene (15 c.c.) was added to an ice-cooled solution of aluminium chloride (4·2 g.) in nitrobenzene (25 c.c.). After being kept at room temperature overnight, the reaction mixture was poured on ice and hydrochloric acid, and freed from nitrobenzene by steam distillation. The residue was extracted with ether, washed with sodium carbonate solution, and the dried solution distilled at 150°/0·2—0·4 mm. A small amount of yellow viscous oil was obtained. This, dissolved in alcohol and treated with Brady's reagent (10 c.c.), gave the 2 : 4-*dinitrophenylhydrazone* of the tricyclic ketone (XX), which crystallised from alcohol in clusters of long orange-red needles, m. p. 242—244° (Found : C, 65·2; H, 5·55; N, 13·8. $C_{22}H_{24}O_4N_4$ requires C, 64·7; H, 5·9; N, 13·7%).

(*b*) A solution of the acid (XIX) (4 g.) in benzene (50 c.c.) was stirred with phosphorus pentachloride (4·2 g.), and to the clear solution of the resulting acid chloride was slowly added a solution of anhydrous stannic chloride (2·35 g.) in benzene (5 c.c.). Stirring was continued for 18 hours, and the product was treated with ice and hydrochloric acid. The benzene solution was washed with sodium carbonate solution, dried, and distilled. The crystalline distillate (1·4 g.), b. p. 160—170°/0·4 mm., was recrystallised from alcohol and had m. p. 67—68° (Found : C, 78·9; H, 8·5. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%). This substance had the properties of a *lactone* and is doubtless represented by the structure (XXI), the formation of which may be attributed to isomerisation of unsaturated acid which had resisted hydrogenation to (XIX).

A number of other cyclisation experiments were carried out, but the desired ketone (XX) was not obtained in satisfactory yield.

2-*Benzylcyclopentylacetic Acid*.—This acid was prepared from ethyl *cyclo*pentanone-2-carboxylate (Cornubert and Borrel, *Bull. Soc. chim.*, 1930, **47**, 301) by the 8-stage procedure of Duff and Ingold (J., 1934, 87). Hydrolysis of the intermediate ethyl α-benzyladipate was more satisfactorily effected by boiling alcoholic potash than by the acid hydrolysis method of Duff and Ingold.

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-*Octahydro*-5 : 6-*benz*-7-*azulone* (XXIII).—Phosphorus pentachloride (9·5 g.) was added to a stirred solution of 2-benzyl*cyclo*pentylacetic acid (9·5 g.) in benzene (110 c.c.). When a clear solution was obtained, the benzene and phosphorus oxychloride were removed by heating on the water-bath under reduced pressure. The residual chloride, dissolved in carbon disulphide (90 c.c.), was treated with powdered anhydrous aluminium chloride (6·6 g.). When the vigorous evolution of hydrogen chloride had subsided, the whole was heated on the water-bath for 8 hours. The aluminium chloride complex was decomposed with ice and hydrochloric acid, and the product was distilled in steam. After the carbon disulphide had been driven off, a white solid slowly collected in the steam distillate; more was extracted with ether from the aqueous distillate. This *octahydrobenzazulone* (XXIII) (6·4 g.) crystallised from methyl alcohol in colourless prisms, m. p. 56° (Found : C, 84·0; H, 7·9. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Its 2 : 4-*dinitrophenylhydrazone* formed small orange prisms (from ethyl acetate), m. p. 169—170° (Found : N, 14·7. $C_{20}H_{20}O_4N_4$ requires N, 14·7%).

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-*Octahydro*-5 : 6-*benz*-7-*azulol* was obtained in theoretical yield by reduction of the ketone (XXIII) with aluminium *iso*propoxide (compare Lund, *Ber.*, 1937, **70**, 1520). It crystallised from ligroin in a fine matte of colourless needles, m. p. 128—129° (Found : C, 83·2; H, 8·8. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%). An attempt to obtain benzazulene by heating this carbinol with selenium at 300° led to polymerisation, the product being mostly non-volatile in a high vacuum. When the carbinol (3·4 g.) was heated at 160° for an hour with potassium hydrogen sulphate (7 g.), it gave 1 : 2 : 3 : 4 : 9 : 10-hexahydrobenzazulene (2·7 g.), b. p. 130—135°/1 mm. The distillate solidified to a mass of crystals, m. p. 29—35°. Hydrogenation of this unsaturated hydrocarbon to *octahydrobenzazulene* (XXIV) was effected by palladium-black in alcoholic solution. The resulting oil crystallised in the refrigerator, giving fine needles, which after recrystallisation from alcohol had m. p. 29—30° (Found : C, 90·2; H, 9·7. $C_{14}H_{18}$ requires C, 90·3; H, 9·7%).

Attempted Dehydrogenation of 1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-*Octahydrobenzazulene* (XXIV).—(*a*) A mixture of the hydrocarbon (1 g.) and selenium (1·7 g.) was heated in an atmosphere of carbon dioxide for 29 hours. The distilled product was a brownish liquid which gave no addition compound with *s*-trinitrobenzene.

(*b*) A mixture of the hydrocarbon (1 g.) and palladium-black (0·1 g.) was heated in an atmosphere of carbon dioxide, first at 250° for 3 hours and then at 300° for 4 hours. Distillation of the product gave a violet liquid (0·5 c.c.), b. p. 110—120°/1 mm., but the feeble intensity of colour suggested that the amount of azulene present was very small.

(*c*) The hydrocarbon (1 g.) was heated with palladium-black as described under (*b*), except that the evolved gas was collected over 50% potassium hydroxide solution. Only 16 c.c. of gas were collected after 3 hours' heating at 300°, showing the almost complete absence of dehydrogenation. The activity of the catalyst was subsequently demonstrated by the fact that it rapidly liberated the theoretical amount of hydrogen from *s*-octahydroanthracene at 300°.

We express our thanks to the Carnegie Trust for the Universities of Scotland, for a grant for the purchase of a hydrogenation autoclave, and to Dr. E. de Barry Barnett for a gift of *s*-octahydroanthracene. We are also indebted to Dr. R. Wright for advice on the determination of densities of fused hydrocarbons.

UNIVERSITY OF GLASGOW. [*Received, January 14th*, 1944.]

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77. *Derivatives of Monosilane. Part III. The Fluoromonosilanes.*

By H. J. EMELÉUS and A. G. MADDOCK.

Experiments on the fluorination of certain halogenated silanes are described. Mono-, di-, and tri-fluoromonosilane have been prepared and characterised.

Two fluoromonosilanes are on record. Tetrafluoromonosilane or silicon tetrafluoride was known to Scheele and has been exhaustively studied by a number of other workers since. Trifluoromonosilane or silicofluoroform has been described in but three previous papers. Ruff and Albert (*Ber.*, 1905, **38**, 53, 2222) prepared silicofluoroform by the action on silicochloroform of titanium tetrafluoride. The product was analysed, and characterised by determination of the m. p. and b. p. Those authors also described a thermal decomposition involving the formation of silicon tetrafluoride, silicon, and hydrogen. Later, Booth and Stillwell (*J. Amer. Chem. Soc.*, 1934, **56**, 1531) prepared silicofluoroform by reaction between silicochloroform and antimony trifluoride.

They revised Ruff and Albert's physical data and reported that silicofluoroform suffered a slow disproportionation, giving silicon tetrafluoride and monosilane, even at very low temperatures. A further observation bearing on the fluorosilanes was Moissan and Smiles's report (*Compt. rend.*, 1902, **134**, 1549) that disilane reacts vigorously with sulphur hexafluoride to give undetermined products.

Direct fluorination, either by a diluted fluorine stream or by the use of those fluorinating agents, such as cobaltic fluoride, which act by virtue of a small dissociation pressure of fluorine, seemed unlikely to yield the partly fluorinated monosilanes. It was therefore decided to investigate the fluorination of the chloro- and iodo-monosilanes by mercurous, silver, and antimony fluorides.

Experimental.

Most of the reactions now described were carried out in a Stock-type universal vacuum apparatus. The mercurous fluoride was prepared according to Henne and Renoll (*J. Amer. Chem. Soc.*, 1938, **60**, 1060). Silver fluoride solution was prepared by dissolution of silver carbonate in 40% hydrofluoric acid solution in the dark, the solution being evaporated in a platinum dish in diffuse daylight with constant stirring. Thus prepared, silver fluoride was obtained as an orange-brown, granular powder, possessing great activity as a fluorinating agent. The antimony trifluoride used was a commercial product purified by sublimation in a platinum apparatus. Mono- and di-chloromonosilane were prepared as described by Emeléus and Miller (J., 1939, 819): equal volumes of tensimetrically pure hydrogen chloride and monosilane were heated for 24 hours at 100° in a globe in the presence of anhydrous aluminium chloride, and the products were separated by a series of fractional distillations and condensations. Trichloromonosilane (silicochloroform) was formed as a minor product in this reaction, but its preparation in this manner was uneconomical. It was prepared in larger quantities by the action of hydrogen chloride on silicon at 400°; the gases formed were condensed in an acetone–solid carbon dioxide bath, and the trichloromonosilane separated from the silicon tetrachloride, first by a fractional distillation at atmospheric pressure with a long still head, and subsequently by further fractional distillations and condensations in the vacuum apparatus. Mono- and di-iodomonosilane were prepared by a method already described (J., 1941, 353).

The fluorination of silicochloroform by means of antimony trifluoride as described by Booth and Stillwell (*loc. cit.*) was first investigated with a view to determine some further details of the reaction mechanism. The silicochloroform was prepared as described above, the final purification consisting of a distillation at — 70° followed by a condensation at —80°. The product was found to be tensimetrically identical with that of Booth and Stillwell. 2·093 G. of this product were distilled backwards and forwards at room temperature (10—15°) for 3 hours over 5 g. of antimony trifluoride in the presence of 0·2 c.c. of antimony pentachloride; investigation of the products then showed that 1·95 c.c. of hydrogen had been formed. During the fluorination a black film formed over the walls of the vessel and the surface of the antimony trifluoride; this was examined and shown to be metallic antimony. The formation of the film is due to the appreciable volatility of antimony trifluoride at room temperature: such a metallic film has been shown to be formed in all cases with antimony trifluoride where oxidising fluorination is possible, the probable reaction being represented by the equation $6SiHCl_3 + 8SbF_3 = 3H_2 + 6SiF_4 + 2Sb + 6SbCl_3$, *i.e.*, it may be measured by the hydrogen and silicon tetrafluoride formed. The ratio 1 : 2 of these gases was verified experimentally.

The fluorinated products were separated by fractional distillation at —120° and by condensation at — 155° and in liquid nitrogen. The residue was further fractionated, and 0·750 g. of tensimetrically pure silicochloroform recovered. A head fraction from this separation was combined with the condensate at — 155°, and the mixture resolved by further fractionations into a less volatile fraction, consisting of partly fluorinated compounds, and a more volatile fraction (4·0 c.c.) characterised by vapour-pressure determinations as silicon tetrafluoride. The most volatile fraction was easily fractionated to tensimetric homogeneity, 158 c.c. of the product being obtained. Analysis by decomposition with sodium hydroxide showed it to consist of silicofluoroform. The freshly prepared product had a sharp m. p. and the mean of four determinations gave m. p. — 131·4° (ethylene thermometer). The following observations were made on the vapour pressure of the freshly isolated product:

Temp.	—105·0°	—108·0°	—110·0°	—112·5°	—114·0°	—117·0°
Press., mm. Hg	352	275	222	175	145	125

From these data the b. p. is — 95·0°, and the latent heat 4802 cals. Trouton's constant is 27·0, indicating considerable association in the liquid phase.

The steady decomposition by disproportionation at room temperature reported by Booth and Stillwell was observed, but this decomposition did not continue at the temperature of liquid nitrogen, as reported by these authors. The vapour pressure of the compound rises progressively and, in view of the disproportionation of difluoromonosilane reported below, it seems probable that the reaction is a simple disproportionation to monosilane and silicon tetrafluoride.

In the above experiment about 75% of the silicochloroform was converted into silicofluoroform, about 2% transformed into silicon tetrafluoride by oxidising fluorination, and the residual silicochloroform converted into partially fluorinated products, in particular dichloromonofluoromonosilane. These figures are calculated on the silicochloroform reacting and not on the quantity taken, 28% of which was recovered unchanged. In other experiments longer periods of reaction were allowed and in this way more complete conversion could be obtained. With 24 hours' treatment, all the silicochloroform reacted and 91% of the theoretical yield of silicofluoroform was obtained, but the extent of the oxidising side reaction also rose to 8%. In each case the reaction took place at room temperature.

In view of the satisfactory result of the above fluorination, the action of antimony trifluoride on tensimetrically pure dichloromonosilane (silylene chloride) was investigated. A preliminary test showed that a reaction took place at room temperature with considerable blackening of the antimony trifluoride, formation of an antimony mirror, and the evolution of hydrogen. A series of quantitative experiments were then carried out in which measured volumes of silylene chloride were fluorinated with an excess of antimony trifluoride in the presence of 10% of antimony pentachloride at room temperature for various times. The results were closely analogous to those with silicochloroform, but the reaction was rather slower and, if it was allowed to continue, progressively more oxidising fluorination took place. A reaction time of about 24 hours gave the greatest yields of silylene fluoride when using about 200 c.c. of dichloromonosilane with 5 g. of antimony trifluoride. The product, from such a preparation, was readily resolved into five fractions: (i) about 10%, calculated on the volume of silylene chloride taken, consisted of hydrogen; (ii) volatile at — 160°, was about 0·5%, and probably consisted of silicofluoroform from the oxidising fluorination; (iii), the largest, constituting about 90% by volume, volatile at — 130°, consisted of silylene fluoride and silicon tetrafluoride (80% and 10%, respectively) and traces of unidentified products assumed to be partly fluorinated compounds; (iv) a small fraction of about 8—9% of partly fluorinated compounds distilling at — 100°; (v) residue, 0·5—1%, of unchanged silylene chloride. Longer periods of fluorination increased the quantity of hydrogen and silicon tetrafluoride up to 30%. It is thus seen that under favourable conditions yields of silylene fluoride up to 80% could be obtained. The yield of the reaction could rapidly be determined

by fractionation into the distillates mentioned above, and thence calculated from the volume of hydrogen formed and the volume of the third fraction. As a further check a sample of the third fraction was quantitatively decomposed with sodium hydroxide, silylene fluoride reacting according to the equation $SiH_2F_2 + 4NaOH = H_2O + 2H_2 + Na_2SiO_3 + 2NaF$. The silicon tetrafluoride reacts without production of a permanent gas. The presence of any chlorine derivatives in the product could be tested for in this hydrolysed mixture.

At first, this method of analysis gave anomalous results, but it was found that this was due to incomplete reaction of the alkali with the silylene fluoride, resulting in the formation of rather stable hyposilicates, such as Schwarz has described, which decompose on heating in water with the evolution of hydrogen. A more precise and standardised procedure eliminated this difficulty. About 15 c.c. of the silylene fluoride sample was distilled on to about 10 c.c. of previously degassed 30% sodium hydroxide solution cooled in liquid nitrogen and contained in a bulb tube closed by a tap. The tap was closed, and the alkali boiled for some time (30 mins.) by placing the vessel in water at 35—40°. The hydrogen formed was pumped off by a Töpler pump through a trap cooled in liquid nitrogen, and measured in the gas burette. The reaction was thus taken to completion.

Numerous quantitative preparations were subsequently carried out, and in all the yield of silylene fluoride was about 80% under the conditions described above. The isolation of pure silylene fluoride from the silicon tetrafluoride in the third fraction proved less easy than was expected. An initial mistake was made in supposing that silylene fluoride should be more volatile than silicon tetrafluoride. By following an attempted separation by the above method of analysis it was soon shown that this was not the case. Eventually by a series of fractional distillations at − 130°, combined with fractional condensations at − 143°, a pure sample of silylene fluoride was isolated. In view of the difficulty of this separation and the low yield of the fourth fraction no attempt was made to isolate a partially fluorinated product such as SiH_2ClF.

The analysis of the final product was made by hydrolysis in the manner described above, combined with a determination of the fluorine in the hydrolysed mixture by De Boer and Basant's method (*Z. anorg. Chem.*, 1926, **152**, 213). Analytical results are given below. Three determinations of the vapour density by direct weighing gave the values of

Vol. of SiH_2F_2 taken, c.c. at N.T.P.	Vol. of H_2 formed, c.c. at N.T.P.	H_2/SiH_2F_2. Found.	Calc.	Fluorine, %. Found.	Calc.
12·55	25·0	1·99	2·00	56·3	55·9
16·18	32·0	1·98	2·00	56·7	55·9
17·50	34·7	1·98	2·00	56·0	55·9

68·3, 68·5, 68·7 (Calc. : 68·0). The mean of four determinations of the m. p., using an ethylene thermometer, gave it as − 122·0°, and this was confirmed by the intersection of the two branches of the vapour-pressure curve determined in the usual manner by using ethylene and hydrogen chloride vapour-pressure thermometers. The data are given below, and lead to a b. p. of − 77·8° and a latent heat of 4751 cals. Hence Trouton's constant = 25·7, indicating considerable association in the liquid phase. This fact is in agreement with the anomalous b. p.

Temp.	− 85·2°	− 88·2°	− 88·5°	− 90·9°	− 93·0°	− 95·0°	− 97·7°	− 99·8°	−105·0°
Press., mm. Hg	463·0	417·4	396·3	332·1	296·0	250·3	197·3	169·0	121·4
Temp.	−106·9°	−112·2°	−116·2°	−118·1°	−120·8°	−124·2°	−129·3°	−132·5°	−134·5°
Press., mm. Hg	101·7	60·9	41·6	37·7	25·5	16·5	11·0	8·2	6·1

The difficulty in the separation of the silylene fluoride from the crude product made an investigation of alternative preparations desirable, and analogy with the corresponding carbon compounds suggested an attempt to fluorinate silylene iodide with silver or mercurous fluoride. However, in neither case was the result satisfactory. In the first case silylene iodide was allowed to melt in contact with silver fluoride cooled in ice, but even at this low temperature a violent reaction took place, giving a red flame and formation of a brown amorphous powder. A large volume of hydrogen was also formed. In the second case the silylene iodide reacted quite smoothly with the cooled mercurous fluoride, but a considerable volume of hydrogen was formed and by measurement of its volume a limit of 55% was set to the maximum possible yield of silylene fluoride. Further examination of this preparation was therefore postponed.

Owing to the instability of silicofluoroform (see above), the stability of silylene fluoride was examined. No appreciable change in the vapour pressure of a sample of silylene fluoride stored over mercury for 14 days was noticed; however, the vapour pressure of a sample of silylene fluoride stored in the same manner for two years (room temperature, 0—20°) was found to have risen considerably. A series of fractional condensations at − 160° resolved the mixture thereby formed into equal volumes of silicon tetrafluoride and monosilane. Complete disproportionation had therefore taken place : $2SiH_2F_2 = SiH_4 + SiF_4$.

The preparation of monofluoromonosilane or silyl fluoride by fluorination of silyl chloride by antimony trifluoride was next examined. Preliminary experiments showed that fluorination took place at room temperature, again with the formation of an antimony mirror and the evolution of hydrogen. In one of a number of quantitative experiments, 201 c.c. of silyl chloride were confined over 5 g. of antimony trifluoride mixed with 0·2 c.c. of antimony pentachloride for 24 hours at 12°; 45 c.c. of hydrogen and 142 c.c. of products volatile at − 130° were obtained. The residue, all of which distilled above − 80°, was shown tensimetrically to consist almost entirely of unchanged silyl chloride. This indicates a 79% yield of silyl fluoride in the more volatile fraction on the assumption that little silylene fluoride or silicofluoroform was formed. A similar conclusion was reached from the results of analysis of samples of the − 130° fraction by hydrolysis with sodium hydroxide. Longer periods of fluorination were again found to produce more hydrogen and consequently more oxidising fluorination.

The separation of pure silyl fluoride from the product of the above fluorination proved very difficult, and a degree of purity exceeding 98% could not be attained. It is thought that the isolation of silyl fluoride is rendered difficult by a slow disproportionation reaction which is more rapid than those observed with the other fluorides. It was, indeed, soon observed that samples stored at room temperature steadily increased in vapour pressure. Fractionations on quantities as large as 2 l. of gas were carried out, and a series of fractional distillations at − 140° with condensation of the silicon tetrafluoride proved most effective. The course of the fractionation was followed by vapour-density measurements and analysis. Attempts to obtain a more readily purified product by fluorination of silyl iodide by mercurous or silver fluoride were as unsuccessful as the experiments with silylene iodide : the results indeed were closely analogous. Analysis of the purest sample of silyl fluoride obtainable gave the results shown below.

Vol. of SiH_3F taken, c.c. at N.T.P.	Vol. of H_2 found, c.c. at N.T.P.	H_2/SiH_3F. Found.	Calc.	Fluorine, %. Found.	Calc.
21·2	62·4	2·94	3·00	40·8	38·0
17·1	50·1	2·93	3·00	41·0	38·0

Observed values of the vapour density were 51·0, 51·1 (Calc.: 50·5). A few points on the vapour pressure curve were determined, and are tabulated below.

Vap. press., mm. Hg	58	100	184	243	320	416
Temp.	−128·1°	−122·0°	−116·2°	−112·5°	−109·1°	−105·8°

The extrapolated b. p. is − 98·6°, and the latent heat 4500 cals. This gives 25·8 for Trouton's constant, again indicating the association of these compounds in the liquid phase.

The fluoromonosilanes appear, therefore, to be characterised by anomalous b. p.'s due to association in the liquid phase, caused presumably by hydrogen bonds, and by a pronounced tendency to disproportionation even at room temperature which is most marked in the case of silyl fluoride and silicofluoroform.

IMPERIAL COLLEGE, LONDON, S.W.7. [*Received, December 8th*, 1943.]

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78. *α-Methylenic Reactivity in Olefinic Systems. Part I. The Prins Reaction with Propylene.*

By JOHN W. BAKER.

Propylene reacts with paraformaldehyde in the presence of a mixture of 100% acetic and sulphuric acids at 35° to give (1) the diacetate of *n*-butane-1 : 3-diol (63·5%), (2) the cyclic *formal* (14%) of this diol, and (3) 4-*acetoxytetrahydro-γ-pyran* (22·5%). The first two products arise from an acid-catalysed addition to the double bond, but the third, which is not formed by the further reaction of the diol with formaldehyde, involves the direct reaction of the hydrogen of the methyl group of propylene, activated by its conjugation with the olefinic linking. The rate of absorption of each of the reaction ingredients during the course of the reaction has been determined, and mechanisms for the formation of the products are suggested on the basis of these results.

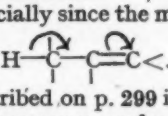
THE inclusion of " no-bond " structures of the type $\overset{+}{H}\,C{=}C{-}\overset{-}{C}$ in the resonance hybrid representing systems, $H{-}\overset{\curvearrowright}{C}{-}C{=}\overset{\curvearrowright}{C}$, in which a H–C bond is conjugated with an unsaturated (olefinic) system, was suggested by Baker and Nathan (J., 1935, 1847), and both the polarisability (electromeric) effect (cf. *inter alia*, Baker and Nathan, *ibid.*, p. 1844; Baker, *Trans. Faraday Soc.*, 1941, **37**, 632; Hughes, Ingold, and Taher, J., 1940, 949) and the polarisation (mesomeric) effect (Baker and Hemming, J., 1942, 191) of alkyl groups arising therefrom, have been experimentally established. The validity of such electron displacement is now generally accepted (cf. Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 674) but the experimental investigations have, hitherto, been restricted mainly to examples in which the H–C bonds are conjugated with an aromatic nucleus. Theoretically, no such restriction is applicable, and it is evident that the postulated " no-bond " resonance structures should give rise to increased reactivity of such α-methylenic hydrogen atoms, possibly smaller in magnitude than, but in no sense different in character from, that which arises from suitable conjugation with other activating unsaturated groups such as carbonyl, $H{-}\overset{\curvearrowright}{C}{-}C{=}\overset{\curvearrowright}{O}$, or cyano, $H{-}\overset{\curvearrowright}{C}{-}C{\equiv}\overset{\curvearrowright}{N}$. Indeed, evidence for such α-methylenic activity in olefinic and polyolefinic systems is accumulating from the investigations of Farmer and his collaborators in the reactions of such hydrocarbons with maleic anhydride (*Trans. Faraday Soc.*, 1942, **38**, 340) and saligenin (Cunneen, Farmer, and Koch, J., 1943, 472), in the mechanism of autoxidation of rubber and drying oils, and in the rearrangement of double bonds during such autoxidations (Farmer, *Trans. Faraday Soc.*, 1942, **38**, 348, 356; Farmer, Koch, and Sutton, J., 1943, 541).

A further interesting example is adumbrated in the claim made (B.P. 545,191, 1942) that olefins of the type $R^1R^2C{:}CR^3{\cdot}CH_3$ (R^3 = alkyl, alicyclic, alphyl or aryl; R^1, R^2 = the same or hydrogen) react at room temperature with trioxymethylene in the presence of catalysts such as stannic chloride, zinc chloride, zinc dichloroacetate, etc., in dry, inert solvents such as ether, chloroform, or saturated hydrocarbons to give unsaturated alcohols of the type $CR^1R^2{:}CR^3{\cdot}CH_2{\cdot}CH_2{\cdot}OH$. It is specifically stated that the catalyst should be " non-acidic " under the reaction conditions employed, and this is of particular interest in relation to the reaction known to occur between some olefins and trioxymethylene in the presence of acetic–sulphuric acids. Under such conditions Prins (*Chem. Weekblad*, 1919, **16**, 1510) found that the main products are the diacetate $CR_2(OAc){\cdot}CR_2{\cdot}CH_2{\cdot}OAc$ of the 1 : 3-diol, together with the corresponding cyclic formal $CR_2\langle\begin{smallmatrix}CR_2{\cdot}CH_2\\O{-}CH_2\end{smallmatrix}\rangle O$. Thus, whereas under the conditions of the Prins reaction, a normal, acid-catalysed addition to the olefinic linking occurs (see below), the not very dissimilar conditions described in the patent are stated to give rise to reaction at the α-methylenic hydrogen atom.

In this series of papers it is proposed to investigate to what extent the typical reactions of " normally " activated hydrogen may be paralleled by similar reactions in which the activation of the hydrogen is dependent solely on its conjugation with an olefinic system. The present communication deals with a further study of the products formed in, and the mechanism of, the Prins reaction.

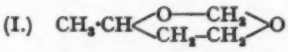
In his original investigation with styrene, Prins allocated the symmetrical structure $CHPh(CH_2{\cdot}OAc)_2$ to the diacetate formed, but Fourneau, Benoit, and Firmenich (*Bull. Soc. chim.*, 1930, **47**, 860) later proved that the correct structure is $CHPh(OAc){\cdot}CH_2{\cdot}CH_2{\cdot}OAc$, since cinnamyl alcohol was isolated from the hydrolysis products of Prins's diacetate. Extension of the Prins reaction to certain simple olefins has been briefly described, mainly in the patent literature. Preliminary investigations on the reaction of a number of simple olefins and

olefinic compounds with formaldehyde under the conditions of the Prins reaction were carried out by Drs. H. Gudgeon and D. B. Kelly, of Messrs. Imperial Chemical Industries, Ltd. (Dyestuffs Division). The results obtained showed that, of such olefins, propylene is a very suitable compound for further study, since it is rapidly absorbed by a mixture of trioxymethylene in an acetic–sulphuric acid medium at 35° to give good yields of water-insoluble products. These were shown to contain the diacetate of a C_4 diol and the corresponding cyclic formal, but the exact constitutions of the products were not definitely established.

It was decided, therefore, to investigate this reaction more fully, especially since the methyl-group hydrogen atoms are potentially activated by conjugation with the olefinic linking,  .

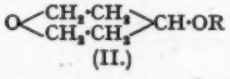
The clean mixture of products obtained by using the conditions described on p. 299 is readily separated by fractional distillation through an effective column. In this manner three pure products were isolated; (I), b. p. 29°/24 mm.; (II), b. p. 47·5°/1 mm.; (III), b. p. 65°/1 mm., the average composition of the total, isolated pure products being 14, 22·5, and 63·5% respectively.

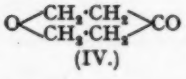
Products (I) and (III) (previously isolated in an impure condition by Gudgeon and Kelly) are the analogues of those obtained by Prins in the corresponding reaction with styrene, and are, respectively, the cyclic *formal* (I) and the diacetate (III) of *n*-butane-1 : 3-diol.

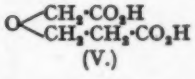
(I.)  $CH_3{\cdot}CH(OAc){\cdot}CH_2{\cdot}CH_2{\cdot}OAc$ (III.)

Evidence for the structures assigned to the products is detailed on p. 300: (I) is hydrolysed by 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid to give formaldehyde-2 : 4-dinitrophenylhydrazone and *n*-butane-1 : 3-diol, and (III) is hydrolysed in alkaline solution to the same diol and a metal acetate. In both cases the diol was characterised by conversion into its di-*p*-nitrobenzoate, m. p. 103°, and its *di-α-naphthylurethane*, m. p. 153°, identical with specimens prepared from the genuine diol. Moreover, pyrolysis of (III) at 550° (kindly carried out by Messrs. Imperial Chemical Industries, Ltd.) gave a 50·9% yield of butadiene, closely approximating to that (52·7%) obtained from a genuine synthetic specimen of the diacetate under identical conditions. (I) and (III) thus represent the normal products of the additive reaction at the ethylenic linking.

The greatest interest from the point of view of the main object of this series of investigations attaches to the new *product* (II). This is a fragrant liquid of composition $C_7H_{12}O_3$ (II, R = Ac). Hydrolysis with cold alkali shows that it contains one acetoxy-group per molecule and converts it into a secondary *alcohol* $C_5H_{10}O_2$ (II, R = H). Oxidation of this with potassium dichromate and sulphuric acid gives a ketone $C_5H_8O_2$, identical with tetrahydro-γ-pyrone (IV) obtained by Borsche (*Ber.*, 1915, **48**, 683; 1923, **56**, 2012). Oxidation of either (II) or (IV) with nitric acid affords β-carboxymethoxypropionic acid (V), m. p. 97°, identical with the acid, m. p. 93—94°, obtained by Borsche by oxidation of tetrahydro-γ-pyrone with potassium permanganate. This acid was shown by direct comparison not to be identical with either β-hydroxyglutaric acid, m. p. 95°, or α-carboxymethoxypropionic acid, m. p. 69° (Jungfleisch and Godchot, *Compt. rend.*, 1907, **145**, 71, give m. p. *ca.* 30°) which would be obtained from other possible structures for (II). Moreover, the structure of (V) was confirmed by its conversion into β-iodopropionic acid by hydrolysis with hydriodic acid; it has been characterised by conversion into its *diamide*, m. p. 174°, its *methyl ester monoamide*, m. p. 77°, and its *dimethyl* ester, b. p. 138°/24 mm.


(II.)


(IV.)


(V.)

Before discussing the mechanism of the formation of (II), reference must be made to the results of a kinetic study of the course of the reaction. By methods described on p. 299 the reaction between propylene and paraformaldehyde in homogeneous solution in acetic–sulphuric acid medium was followed: determination of (1) total acidity, by titration, and (2) sulphuric acid, by gravimetric determination as barium sulphate, together gave the rate of absorption of acetic acid; (3) absorption of formaldehyde was followed by gravimetric determination as its 2 : 4-dinitrophenylhydrazone; (4) propylene absorption was found by direct measurement from a graduated gasometer. The results, summarised in Table I, are shown in the figure.

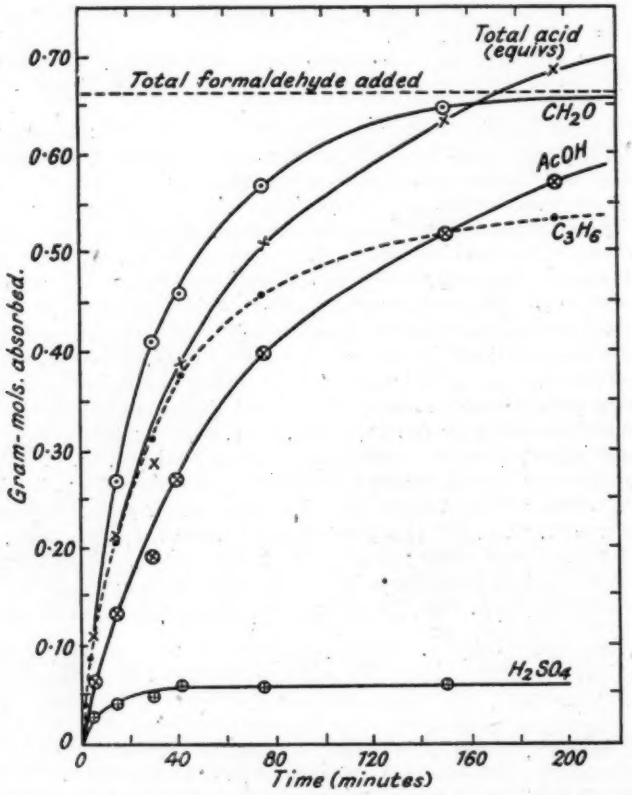
TABLE I.

	Time (mins.).	C_3H_6 absorbed (g.-mol.).	CH_2O absorbed (g.-mol.).	AcOH absorbed (equiv.).	H_2SO_4 absorbed. Equiv.	H_2SO_4 absorbed. G.-mol.	Total acid absorbed (equiv.).
Original	0	0	0·663	2·659	0·572	0·286	3·231
	5	0·116	—	0·063	0·058	0·029	0·121
	15	0·205	0·267	0·133	0·082	0·041	0·215
	30	0·310	0·407	0·190	0·096	0·048	0·286
	41	0·376	0·456	0·269	0·114	0·057	0·383
	75	0·457	0·567	0·397	0·110	0·055	0·507
	150	0·517	0·645	0·517	0·115	0·057	0·632
	195	0·533	—	0·569	—	—	0·684
Unused	—	—	0·018	2·090	0·457	0·229	2·547

All figures refer to a 200 c.c. sample.

In view of the complicated nature of the reaction (it is probable that the three products are formed in separate, concurrent reactions), a detailed kinetic analysis is not possible, but several features are worthy of note.

At an early stage (*ca.* 30 mins.) the quantity of sulphuric acid absorbed attains a value which then remains constant throughout the remainder of the reaction. This suggests the formation of an intermediate which subsequently remains in equilibrium with free sulphuric acid. The difficulty inherent in such a suggestion is that any intermediate must be of a character such that it cannot be precipitated as barium sulphate after dilution of the reaction medium. Alternatively, the early absorption may depend on a side reaction such as the formation of a hydroxy-sulphonate, $CH_3 \cdot CH(OH) \cdot CH_2 \cdot SO_3H$, at an initial rate comparable to that of the olefin–formaldehyde reaction, but which is rapidly suppressed as the latter reaction becomes of preponderating importance. The subsequent, constant concentration of the sulphuric suggests that, in the main reactions, it functions purely as an acid catalyst for the additive reactions to the carbonyl group in formaldehyde, *e.g.*, $CH_2{:}O + H_2SO_4 \rightleftharpoons CH_2{:}\overset{+}{O}H + \overset{-}{H}SO_4$. The molecular ratio, formaldehyde absorbed/olefin absorbed,



(*Note*: *Values for the acids absorbed at 30 mins. are known to be slightly low.*)

rapidly attains a value > 1, in harmony with the fact that two out of the three products formed require a molecular ratio $2CH_2O/1C_3H_6$.

The lag in the absorption of acetic acid in the earlier stages is explained partly by the formation of the formal (in the production of which acetic acid plays no part) and partly by the slower acetylation of the hydroxy-monoacetate (VI) which is, presumably, the initial product in the ultimate production of (III). The following scheme for the formation of (I) and (III) is in harmony with the experimental data:

$$CH_2{:}O + H_2SO_4 \rightleftharpoons CH_2{:}\overset{+}{O}H + \overset{-}{H}SO_4$$

$$H{-}OAc,\ CH_2{-}CH{=}CH_2,\ CH_2{=}\overset{+}{O}H \longrightarrow [\overset{+}{H}\ CH_2{\cdot}CH(OAc){\cdot}CH_2{\cdot}CH_2{\cdot}OH] \xrightarrow{AcOH} (III)$$

(VI.)

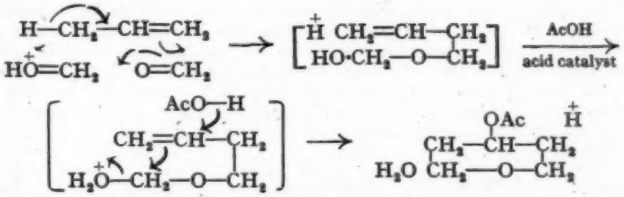
$$CH_2{-}CH{=}CH_2,\ HO{=}\overset{+}{C}H_2,\ O{=}CH_2 \longrightarrow \left[CH_2{-}\overset{+}{C}H{-}CH_2,\ H{-}O{-}CH_2{-}O{-}CH_2\right] \longrightarrow \overset{+}{H} + (I)$$

The formation of the tetrahydro-γ-pyran derivative (II) must involve, at some stage, reaction of a hydrogen of the methyl group in propylene. Further addition of 0·65 g.-mol. of formaldehyde, at the stage when the absorption of the original formaldehyde is practically complete, causes a sudden increase in the rate of propylene absorption, which increase, however, is not long maintained. The composition of the resulting product, *viz.*, (I) 28, (II) 28, (III) 43%, shows an increase in the relative proportions of (I) and (II) formed at the expense of (III), together with a much larger proportion of water-soluble products.

It was at first thought that (II) might be formed by elimination of water from an intermediate (VII) obtained by further condensation, of a hemiacetal type, between (VI) and another molecule of formaldehyde :

$$CH_3{\cdot}CH(OAc){\cdot}CH_2{\cdot}CH_2{\cdot}OH + CH_2O \longrightarrow \underset{\text{(VII.)}}{\left[\begin{matrix}CH_3{\cdot}CH(OAc){\cdot}CH_2\\ HO{\cdot}CH_2{\cdot}O{\cdot}CH_2\end{matrix}\right]} \xrightarrow{-H_2O} \text{(II)}$$

Elimination of acetic acid from (VII) would also provide an alternative route for the production of the formal (I). This hypothesis cannot be maintained since, when the Prins reaction is repeated under identical conditions but with half the original molecular proportion of formaldehyde and *n*-butane-1 : 3-diol in place of propylene, no trace of (II) can be detected in the product, which consists almost entirely of the diacetate (III) together with a little formal (I). It must therefore be concluded that (II) is formed directly from propylene by a route essentially of the following type :



It thus involves the direct reaction of the α-methylenic hydrogen activated by the adjacent olefinic linking.

In the olefin–formaldehyde reaction under the conditions prescribed by the British patent (*loc. cit.*), a cyclic formal [as (I)] is formed together with the unsaturated alcohol. Hence, both in this and in the Prins reaction, the unsaturated linking and the α-methylenic hydrogen are *both* reactive, and the problem of the different course of the reaction, in the two cases, is thus narrowed to the differential functions of the various catalytic conditions on the two possible centres of reactivity. It is hoped that future investigations may throw further light on this aspect.

Finally, an attempt was made to use boron trifluoride as a catalyst for the Prins reaction. The preliminary results in Table II show that this compound in solution (as its complex) in 100% acetic acid is not, in itself, an effective catalyst for the Prins reaction, but it increases the catalytic efficiency of *small* concentrations of sulphuric acid.

TABLE II.

Volume (c.c.) of C_3H_6 absorbed by 10 c.c. of AcOH–BF_3 solution in time, *t*, in the presence of 1 g. of CH_2O + *x* g. of 100% H_2SO_4.*

t (mins.).	*x* = 0·14	0·3	0·42	0·42 (*without* BF_3)
10	18	34	50	32
20	26	51	81	47
30	36	71	108	64
40	44	91	131	79

* Under the conditions of the kinetic experiment 124 c.c. of C_3H_6 were absorbed in 5 mins.

The reaction mixture remains water-white if BF_3–H_2SO_4 is used as a catalyst, whereas it becomes deep brown when high concentrations of sulphuric acid alone are employed.

EXPERMENTAL.

(All micro-analyses were carried out by Drs. Weiler and Strauss, Oxford.)

The propylene used was kindly supplied by Messrs. Imperial Chemical Industries Limited (Dyestuffs Division) and had been prepared by catalytic vapour-phase dehydration of *iso*propyl alcohol over activated alumina at *ca.* 300°. The gas was condensed in a Drikold–ethanol-cooled coil and collected in a cylinder. It was transferred to a graduated 10-l. gas holder, whence it was passed by hydrostatic pressure through calcium chloride drying tubes into the closed glass reaction vessel, contained in a water-tight bath through which water at 35° from a thermostat was circulated. The reaction vessel and bath were suitably mounted on a mechanical shaker. Preliminary experiments showed that the rate of absorption of the propylene by the paraformaldehyde (33 g.)–acetic acid (210 g.)–sulphuric acid (32 g.) mixture, is greatly increased by replacement of ordinary concentrated sulphuric acid by 100% sulphuric acid and, to a smaller extent, by the use of 100% acetic acid in place of ordinary " glacial " acetic acid; the 100% acids were therefore used throughout the investigation. Since the purely preparative runs were carried out essentially in the same manner as the quantitative examination, only the latter is described.

Kinetic Examination.—For a kinetic examination a homogeneous solution (not attained in the initial stages of the preparative experiments) is essential. A mixture of 210 g. of 100% acetic acid, 32 g. of 100% sulphuric acid, and 32 g. of paraformaldehyde was warmed on a steam-bath with constant shaking until an almost homogeneous solution was

obtained. This was freed from a trace of undissolved paraformaldehyde by filtering through glass wool under suction, cooled to 35°, and 200 c.c. of the clear solution were pipetted into the reaction vessel. The latter consisted of a 750-c.c. Pyrex flask fitted with a cork through which passed a lead-in tube for the propylene and a sampling tube fitted with a tap just below a standard glass socket into which was fitted a 2-c.c. pipette with a ground tip. By suitable manipulation of the tap, the reaction mixture could be forced into the pipette by the slight pressure of propylene in the reaction vessel, so a 2-c.c. sample of the reaction mixture could be obtained at any stage in the reaction. The principle of the sampling method was identical with that used by Baker and Hemming (*loc. cit.*) in their examination of the aldehyde–cyanohydrin reaction. All lead-in tubes and the reaction vessel were filled with propylene before the initial gasometer reading was noted, and the absorption was started by setting the shaker in motion. The 2-c.c. sample was diluted to 250 c.c. with distilled water. In 100 c.c. of this diluted solution, *total* acid was determined by titration with 1·915N-sodium hydroxide solution. In another 50 c.c., sulphuric acid was determined gravimetrically as barium sulphate, and thus the acetic acid present was determined by difference. A further 10 c.c. of the diluted solution was pipetted into 50 c.c. of a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid and, after standing overnight in the refrigerator, the separated formaldehyde-2 : 4-dinitrophenylhydrazone was filtered off on a weighed, sintered-glass crucible, washed, and dried over sulphuric acid in a vacuum to constant weight. The composition of the original reaction mixture was initially determined in the same manner. The volume of propylene absorbed was noted by direct reading from the graduated gas-holder, suitable corrections for temperature and pressure being applied. The results obtained have been given in Table I.

Isolation of the Products.—The reaction mixture was neutralised with sodium carbonate decahydrate, the minimum quantity of water being added to prevent the mixture becoming too thick. The resulting mush was extracted once with ether, and the aqueous layer filtered under suction. The separated sodium salts were repeatedly washed, on the Büchner funnel, with ether, and these washings were used to extract the aqueous filtrate. The combined ethereal extracts were washed with water, dried over sodium sulphate, and the ether was removed through a Widmer column. The pale yellow residue was fractionally distilled first through a Widmer column and then refractionated under reduced pressure by means of a 30-cm. complete-reflux, vacuum-jacketed column heated electrically to the appropriate temperature by means of a Sunvic current regulator. The column, packed with 3·5-mm. glass helices (75% single-turn and 25% double-turn spirals) of efficiency equivalent to 6 theoretical plates, was designed and constructed by Dr. I. Dostrovsky (University College) at the Edward Davies Chemical Laboratory, Aberystwyth. The composition of the product was determined by direct weighing of the isolated pure products. The yields thus represent minimum values. Those obtained in the kinetic run are typical and are given below, based on the olefin absorbed :

Propylene absorbed, 0·533 g.-mol.

Products isolated :	(I) Formal	0·059 g.-mol.	= 11%	Total 61% of the theoretical.
	(II) Monoacetate	0·08 ,,	= 15%	
	(III) Diacetate	0·187 ,,	= 35%	

The molecular ratios of the three reactants required for the formation of the three products are theoretically :

Product	(I).	(II).	(III).	Product	(I).	(II).	(III).	Product	(I).	(II).	(III).
C_6H_6	1	1	1	AcOH	0	1	2	CH_2O	2	2	1

On the basis of the product composition, the molecular ratios of acetic acid and formaldehyde absorbed in the actual reaction per molecule of olefin should be 1 : 1·46 : 1·38, the average values observed being 1 : 1·3 : 1·5. In view of the approximate estimate of the composition possible by actual separation and the neglect of small high-boiling residues and water-soluble products, the agreement is satisfactory.

Characterisation of Products.—*4-Methyl-1 : 3-dioxan* (I). This is the most volatile product, b. p. 25°/22 mm. (Found: C, 58·6; H, 9·85. $C_5H_{10}O_2$ requires C, 58·2; H, 9·85%. The *formal* was warmed on a steam-bath with a slight excess of a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, and then kept at room temperature for several days to complete the precipitation of the formaldehyde-2 : 4-dinitrophenylhydrazone. This, after crystallisation from alcohol, had m. p. 166° either alone or mixed with a genuine specimen. The filtrate was made just alkaline with sodium hydroxide, and excess of 2 : 4-dinitrophenylhydrazine was removed by extraction with ether. The residual aqueous liquor was evaporated to dryness on a steam-bath, and the diol extracted with dry acetone. The residue from the acetone solution after evaporation of the solvent was treated with *p*-nitrobenzoyl chloride and aqueous sodium hydroxide. The di-*p*-nitrobenzoate of *n*-butane-1 : 3-diol, after crystallisation from alcohol, had m. p. 103° either alone or mixed with a specimen prepared from a genuine sample of the diol.

n-Butane-1 : 3-diol diacetate (III). This had b. p. 65°/1 mm. (Found: C, 55·5; H, 8·4. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·1%); 0·1587 g. required baryta equivalent to 3·54 c.c. of 0·501N-sulphuric acid for hydrolysis, whence the number of acetyl groups per molecule = 1·95 (calc.: 2·0). A little of the ester was shaken with 50% aqueous sodium hydroxide until a homogeneous solution was formed. This was then shaken with *p*-nitrobenzoyl chloride, and the separated di-*p*-nitrobenzoate was collected and crystallised from alcohol. It had m. p. 103° either alone or mixed with a genuine specimen of *n*-butane-1 : 3-diol di-*p*-nitrobenzoate. The presence of sodium acetate in the original hydrolysis product was established by the usual tests.

The *di-α-naphthyl urethane*, m. p. 153°, after crystallisation from acetone (Found: C, 73·2; H, 5·6. $C_{26}H_{24}O_4N_2$ requires C, 72·9; H, 5·65%), of the diol was prepared in the usual manner from α-naphthyl *iso*cyanate.

4-Acetoxytetrahydro-γ-pyran (II, R = Ac). This had b. p. 47·5°/1 mm. (Found: C, 58·3; H, 8·55; OAc, 40·90. $C_7H_{12}O_3$ requires C, 58·3; H, 8·3; OAc, 40·97%). The *ester* (14 g.) was hydrolysed by keeping at room temperature with 250 c.c. of saturated baryta for 2 hrs., a homogeneous solution resulting. The excess baryta was just neutralised with ½N-sulphuric acid and evaporated to "dryness" on a steam-bath. Anhydrous potassium carbonate was added to the residue, which was then extracted with dry acetone. The acetone solution was dried over anhydrous potassium carbonate. Distillation of the residue from the acetone solution gave *4-hydroxytetrahydro-γ-pyran*, b. p. 60·5/0·7 mm., as a colourless viscous liquid (Found: C, 59·4; H, 9·7. $C_5H_{10}O_2$ requires C, 58·8; H, 9·8%). Its *p-nitrobenzoate* had m. p. 69° after crystallisation from ligroin (b. p. 40—60°) containing a little ether (Found: N, 5·8. $C_{12}H_{13}O_5N$ requires N, 5·6%.

To a mixture of 5 g. of the secondary alcohol, 20 c.c. of water, and 5 g. of concentrated sulphuric acid, 5 g. of sodium dichromate (= 1 atom of oxygen) were added in small successive portions without cooling. The mixture was gently warmed until the colour of the dichromate was destroyed. The cooled mixture was neutralised with anhydrous sodium carbonate, and the product extracted with ether. Distillation of the residue from the dried ethereal solution gave tetrahydro-γ-pyrone, b. p. 73°/20 mm. (Borsche, *loc. cit.*, gives b. p. 67—68°/18 mm.), as a liquid with a pleasant evergreen odour (Found: C, 59·5; H, 8·4. Calc. for $C_5H_8O_2$: C, 60·0; H, 8·0%). It was characterised and identified as its 2 : 4-*dinitrophenylhydrazone*, m. p. 186—187°, after crystallisation from alcohol (Found: C, 47·1; H, 4·3; N, 19·6.

$C_{11}H_{18}O_5N_4$ requires C, 47·1; H, 4·3; N, 20·0%), its 4-phenylsemicarbazone, m. p. 171·5° (Borsche, *loc. cit.*, gives m. p. 169°), and its 2 : 6-dibenzylidene derivative, m. p. 186° (Borsche, *loc. cit.*, gives m. p. 185°).

Oxidation of this ketone, the secondary alcohol, or its acetate with nitric acid (1 : 1) and evaporation of the solution to dryness affords β-carboxymethoxypropionic acid, m. p. 97°, after crystallisation from ether–ligroin (b. p. 40—60°) (Borsche, *loc. cit.*, gives m. p. 93—94°) (Found : C, 40·7; H, 5·40; equiv., by titration, 77·5. Calc. for $C_5H_8O_5$: C, 40·5; H, 5·4%; equiv., 74). The *amide*, prepared through the acid chloride, crystallised from dry alcohol, m. p. 174°, but was difficult to separate from the ammonium chloride (Found : C, 41·6; H, 7·6. $C_5H_{10}O_3N_2$ requires C, 41·1; H, 6·9%). Esterification with methyl alcohol and dry hydrogen chloride gave the *dimethyl* ester, b. p. 138°/24 mm. (Found : C, 48·1; H, 6·9. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8%), converted by methyl-alcoholic ammonia into the above amide, m. p. 174°, and, from the mother-liquor (probably) the *methyl ester amide*, m. p. 73°, after crystallisation from ether (Found : C, 45·6; H, 6·75; N, 8·5. $C_6H_{11}O_4N$ requires C, 44·7; H, 6·8; N, 8·7%).

A small quantity of the acid was warmed with a few c.c. of hydriodic acid (*d* 1·7) for 36 hours on a steam-bath. Evaporation of the liquor gave a residue which crystallised in a vacuum desiccator. Crystallisation from light petroleum (b. p. 40—60°) gave β-iodopropionic acid, m. p. 85° either alone or mixed with a genuine sample.

In agreement with its structure, the $C_5H_8O_5$ acid distilled unchanged without anhydride formation. The m. p. (95°) of β-hydroxyglutaric acid was depressed to 65—85° by admixture with (VI). The isomeric α-carboxymethoxypropionic acid was prepared by the method of Jungfleisch and Godchot (*loc. cit.*), who describe it as having m. p. *ca.* 30°. This acid is exceedingly hygroscopic, but a specimen carefully dried over phosphoric oxide readily crystallised from dry benzene, the m. p. thus being raised to 69°.

Repeated attempts to synthesise β-carboxymethoxypropionic acid by the action of methyl iodoacetate on the sodium derivative of methyl hydracrylate failed, probably because the action of sodium on methyl hydracrylate is more complex than simple substitution at the hydroxyl group. Condensation of ethyl β-iodopropionate with the product of the action of sodium on methyl glycollate afforded ethyl acrylate as the sole product.

Although no specimen of tetrahydro-γ-pyrone was available for direct mixed m. p. comparisons with the derivatives of the ketone $C_5H_8O_2$, the identity of the physical constants with those given by Borsche place its structure beyond reasonable doubt.

Condensation of n-*Butane*-1 : 3-*diol with Formaldehyde in Acetic–Sulphuric Acid Medium.*—The diol (20 g.) was added dropwise with mechanical stirring to a mixture of 88 g. of 100% acetic acid, 11·8 g. of 100% sulphuric acid, and 4·4 g. of paraformaldehyde maintained at 35°. Stirring was continued for 2 hrs., and the product was then neutralised and worked up as in the case of the reaction with propylene. Fractional distillation of the product by means of the column described on p. 300 gave *ca.* 1 g. of the cyclic formal, b. p. 21°/16 mm., and then a sharp rise to the diacetate, b. p. 72—73°/0·8 mm. (12 g.). A further 2·5 g., b. p. 105°/18 mm., were obtained by distillation of the residue and column hold-up from a fractionating Claisen flask. The two diacetate fractions both had Ac, 48·0% (Calc. : 49·4%), and the presence of an acetate in the hydrolysis products was confirmed in the usual manner.

No trace of the monoacetate, b. p. 47·5°/1 mm., was obtained.

Use of Boron Trifluoride as a Catalyst.—Boron trifluoride, prepared by heating a mixture of 69 g. of potassium borofluoride, 10 g. of boric anhydride, and 60 c.c. of concentrated sulphuric acid, was washed with concentrated sulphuric acid saturated with boric anhydride and absorbed in 100% acetic acid. No attempt was made to determine the concentration of boron trifluoride in the fuming liquid thus obtained, but the same solution was used in all the comparative experiments. Propylene was passed from a graduated gas-holder into a solution of 1 g. of paraform in 10 c.c. of this solution to which had been added the appropriate quantity of 100% sulphuric acid. The reaction vessel was shaken in a small, water-tight bath through which water from a thermostat at 35° was circulated. The results are in Table II. The volumes of olefin were not corrected for temperature and pressure in this trial series of experiments.

The author thanks Messrs. Imperial Chemical Industries Ltd. (Dyestuffs Division) for assistance in the prosecution of this work.

THE UNIVERSITY, LEEDS. [*Received, March 21st,* 1944.]

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79. *Spectroscopic Evidence for the* N–H–N *Bond in Ethyleneimine.*

By H. W. THOMPSON and G. P. HARRIS.

The infra-red absorption spectrum of solutions of ethyleneimine in carbon tetrachloride in the region of 3μ has been measured, and the results suggest the occurrence of association through N–H–N bonds. Other experimental results support this conclusion.

SEVERAL workers have discussed the existence of N–H–N bonds. For example, Hunter and his collaborators (J., 1941, 1, 777, 820) have shown, by consideration of the physical properties and molecular weights, that this type of bond probably occurs in pyrazoles, indazoles, amidines, and related compounds. Gordy (*J. Chem. Physics*, 1939, **7**, 170) also found a displacement of the infra-red absorption band of aniline at 2·9μ towards shorter wave-lengths when solutions in inert organic solvents were used, and he attributed this effect to the same cause.

During a recent measurement of the infra-red absorption spectrum of ethyleneimine it was noticed that the absorption band at 3μ due to the NH group is appreciably displaced in wave-length on passing from the vapour to the liquid, whereas other bands are not much affected. The relationships have therefore been examined more closely using solutions in carbon tetrachloride, the spectrum being measured between about 2·9μ and 3·5μ. The results provide strong evidence for the occurrence of hydrogen bonds in this case.

EXPERIMENTAL.

Ethyleneimine, prepared from ethanolamine by Wenker's method (*J. Amer. Chem. Soc.*, 1935, **57**, 2328), was dried over sodium, redistilled, and finally refractionated in a vacuum. Carbon tetrachloride for use as solvent was dried and redistilled.

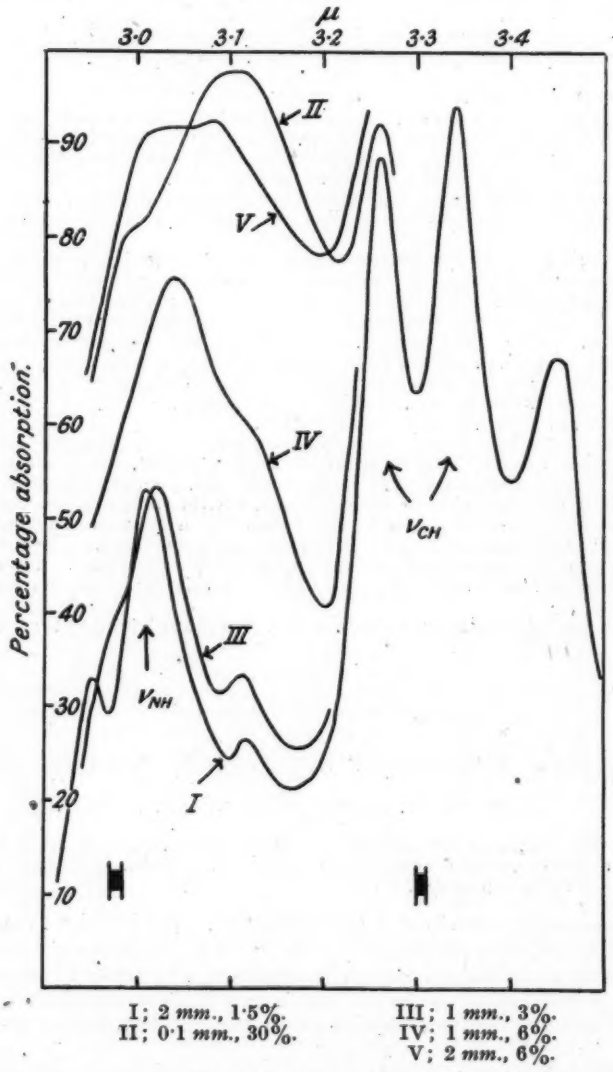
A Hilger D 88 spectrometer with quartz prism was used, with a Hilger–Schwarz compensated vacuum thermocouple

as detector, acting with double photocell amplifier. This very sensitive system made it possible to use narrow slits and thus to obtain fairly high resolving power. The effective slit widths, shown in the figure, were 10—15 cm.$^{-1}$.

The absorption cells were each made by separating a pair of plane polished quartz plates by a metal washer of the required thickness, with seccotine as adhesive.

Results and Discussion.

The results are shown in the figure. Curve I relates to a 2-mm. layer of a 1·5% solution of ethyleneimine in carbon tetrachloride. The three strong absorption bands between 3·2 and 3·5μ are connected with vibrations of 3–H bonds, those at 3·26μ and 3·34μ being probably due to absorption of fundamental valency vibration frequencies, and that at 3·45μ being the overtone of a CH_2 group deformational vibration frequency. The peak at 3·01μ is connected with the N–H stretching vibration.



I; 2 *mm.*, 1·5%. III; 1 *mm.*, 3%.
II; 0·1 *mm.*, 30%. IV; 1 *mm.*, 6%.
V; 2 *mm.*, 6%.

Curve II relates to a 0·1-mm. layer of a 30% solution, these values of concentration and path length being chosen so as to retain the same number of molecules in the absorption path. It can be seen from the curves that, although the position of the C–H band is unaffected, the sharp band at 3·01μ found with the dilute solution gives way at higher concentrations to a broader and more intense band with maximum at about 3·1μ. This effect is precisely similar to those in which an " association " band has been found in the infra-red absorption spectrum of hydroxylic substances. There is a feeble absorption band at about 3·11μ with the dilute solution (curve I) which may be attributed to slight association even at the lowest concentration. The other curves serve to illustrate how the absorption maximum due to the N–H link shifts with increasing concentration. With a thin layer of the pure liquid the effect is even more pronounced.

These results clearly show the occurrence of association through N–H–N bonds with ethyleneimine. Other

arguments support this conclusion. Thus, ethyleneimine boils at 55·5°, *C*-methylethyleneimine at 67°, but *N*-methylethyleneimine at 27·5°. Replacement of the hydrogen atom of the N–H link removes the possibility of a hydrogen bridge, and when there is no association the boiling point is reduced. Measurements (with W. G. Leeds) on the absorption spectrum in the region of 1μ also suggest the formation of hydrogen bonds. The N–H absorption band of liquid ethyleneimine at 0·9μ is very broad, with a weak component on the higher-frequency side. With dilute solutions in carbon tetrachloride or chloroform the broad band is less pronounced and the higher-frequency component sharpens. Another interesting observation is that the displaced line in the Raman spectrum of ethyleneimine due to the N–H vibration frequency appears particularly broad.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, March 29th*, 1944.]

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80. *The Vibrational Spectra of the Vinyl Halides.*

By P. TORKINGTON and H. W. THOMPSON.

The infra-red absorption spectrum of vinyl iodide has been measured between 3 and 20μ. The frequencies of the absorption bands have been correlated with data from the Raman spectrum, and the rotational contour of the infra-red bands has been examined. Magnitudes have been assigned to all twelve fundamental frequencies, and the fundamentals of vinyl chloride, bromide, and iodide have been compared. The variation in magnitude of a given type of mode as the mass of the halogen atom changes is discussed.

IN a previous paper (*Proc. Roy. Soc.*.., in press) we have described the infra-red absorption spectra of vinyl chloride and vinyl bromide, and with the help of data on the Raman spectra a plausible assignment of magnitudes to the normal vibration frequencies has been made. The Raman spectrum of vinyl iodide has already been recorded by Kahovec and Kohlrausch (*Z. physikal. Chem.*, 1940, *B*, **46**, 165). The infra-red spectrum of this substance has now been measured, so that a complete assignment of frequencies can now be made, and the whole array of fundamentals of the vinyl halides can be correlated.

EXPERIMENTAL.

Vinyl iodide was prepared by heating ethylene iodide with a solution of sodium ethoxide in ethyl alcohol (Spence, *J. Amer. Chem. Soc.*, 1933, **55**, 1920). The crude product was washed with dilute sodium bisulphite solution and with water, then dried over calcium chloride and redistilled; b. p. 56°. A small amount of ethyl vinyl ether seemed to be formed as a side reaction. This was removed by washing with cold water and quickly separating off the lower layer of vinyl iodide. The removal of the ether was indicated by the disappearance of its infra-red absorption bands.

For measuring the infra-red spectrum two instruments were used. The first was an automatically recording infra-red spectrometer built in this laboratory, and similar in all essentials to that described in previous papers (Thompson and Harris, *Trans. Faraday Soc.*, in press). A Hilger D 88 spectrometer with fluorite and sylvine prisms, and considerably improved resolving power, produced by the introduction of a Schwarz vacuum thermocouple, was used for the regions 3—7μ and 14—20μ. The absorption cell was a glass tube 20 cm. in length with plane sylvine end-plates. Several pressures of the vapour were used.

RESULTS AND DISCUSSION.

Curves showing the percentage absorption as a function of wave-length are shown in the figure, and the positions of the absorption bands in wave numbers (cm.$^{-1}$) are given in Table I. The Raman displacements recorded by Kahovec and Kohlrausch are given in the same table.

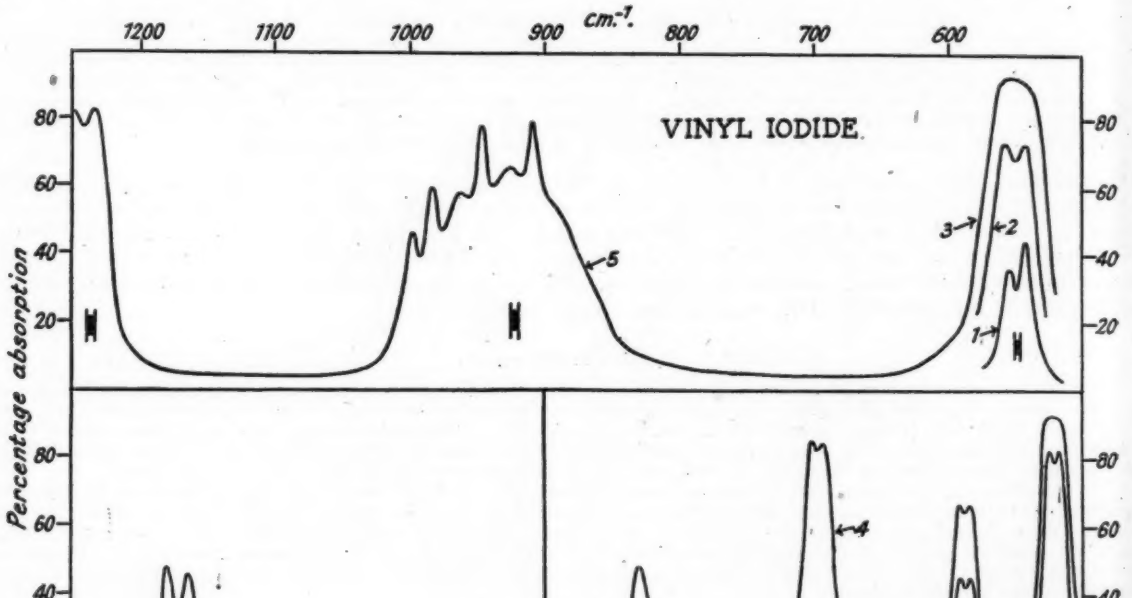
TABLE I.

Infra-red.	Interpretation.	Raman.	Infra-red.	Interpretation.	Raman.
	Fundamental	309	1369 1385 } 1376	Fundamental	1369
	Fundamental	435			
542 557 } 550	Fundamental	535	1412 1438 } 1425	990 + 435	
	2 × 435	879	1456	909 + 550	
909	Fundamental		1587 1600 } 1593	Fundamental	1581
946	Fundamental		1825	2 × 909	
983 997 } 990	Fundamental	982	1862	909 + 946	
	2 × 550	1098	1894	1593 + 309 2 × 946 909 + 990	
1235 1250 } 1242	Fundamental	1229			
1299 1314 } 1307	990 + 309		2242	1242 + 990 Other combinations	
1345	909 + 435		2900	Various combinations	
			2995	Fundamental	3003
			3050	Fundamental	3062
			3115	Fundamental	3092

Vinyl iodide will have nine planar modes of vibration and three non-planar modes, all active in both the Raman and the infra-red spectrum. To a first approximation, the planar vibrations will include three stretching modes, one C=C stretching mode, one C–I stretching mode, and four deformations of the skeleton. These four

deformations can be roughly described as a CH_2 deformation, a CH_2 rocking mode, a bending of the C≡C–I skeleton, and a bending of the odd C–H bond. The three non-planar motions will comprise a twisting vibration and two bending motions.

The molecular structure has been examined by Huggill, Coop, and Sutton (*Trans. Faraday Soc.*, 1938, **34**, 1518), who suggested for the molecular parameters: $r_{CC} = 1{\cdot}34$ A., $r_{CI} = 2{\cdot}03$ A., and $C\widehat{\equiv C}{-}I = 122°$. From these dimensions the three principal moments of inertia will be about 16, 244, and 260 $\times$ 10^{-40} g.-cm.^{2}. The molecule therefore approximates closely to being a symmetrical rotator with moments of inertia 16 and 250 $\times$ 10^{-40}. In the nomenclature of Gerhard and Dennison (*Physical Rev.*, 1933, **43**, 197), $\beta = 14{\cdot}5$, and in that of Badger and Zumwalt (*J. Chem. Physics*, 1938, **6**, 711), $S = -1{\cdot}0$ and $\rho = 14{\cdot}5$. The *P*–*R* spacing of a " parallel " type band would then be about 14 cm.$^{-1}$, and the separation of *Q* branches in a " perpendicular " type would be about 3 cm.$^{-1}$. With the resolving power used in the present work the perpendicular bands will be expected to appear as a strong central peak with a shoulder on each side. The least axis of inertia of the molecule will lie obliquely to the main bond directions, but almost parallel to the C–I bond. Some of the



Path length, 20 *cm.* (1) 20 *mm.*, (2) 50 *mm.*, (3) 140 *mm.*, (4) 140 *mm.*, (5) 25 *mm.*

planar vibrations will therefore in reality have a hybrid rotational contour; the non-planar vibrations should be " perpendicular " in type.

The observed infra-red bands fall fairly sharply into two types. Those at 909 and 946 have the perpendicular structure, and the others are essentially parallel-type bands in which the *P* and *R* branches are separated by the correct spacing and in which the central *Q* branch is not sufficiently prominent to be properly resolved by means of the present instruments. There are some obvious correlations between the infra-red and the Raman data, as shown in Table I, although, as is often found, the Raman frequencies of the liquid tend to be slightly smaller than the corresponding frequencies with the vapour in the infra-red. When both sets of results are considered together with those given previously for the other vinyl halides, the identification of normal frequencies is seen clearly to be the following: 309, 435, 535, 909, 946, 990, 1229, 1376, 1593, ~3000, ~3060, ~3110.

In Table II the frequencies of all the vinyl halides so far examined are collected together. It is hoped shortly to complete the series by measuring the infra-red spectrum of vinyl fluorides; the corresponding data for vinyl cyanide are in course of publication (Thompson and Torkington, this vol.).

Attention should be drawn to one rather striking feature of the correlations in Table II. With three exceptions there is a definite decrease in the frequency of a given vibration as the mass of the halogen atom increases. These three vibrations, ν_7, ν_{11}, and ν_{12}, each involve the deformation of C–H bonds, and in each case there is a small, though probably real, increase in frequency as the mass of the halogen is increased. This may

TABLE II.

Vinyl halides, $CH_2{=}CH{-}X$.

	Type of vibration.		Chloride.	Bromide.	Iodide.
Planar	C–H stretching	ν_1	3030	3014	3000
	C–H stretching	ν_2	3080	3076	3060
	C–H stretching	ν_3	3130	3100	3110
	C=C stretching	ν_4	1610	1605	1593
	C–X stretching	ν_5	724	615	535
	C–X deformation	ν_6	395	345	309
	CH_2 deformation	ν_7	1370	1377	1376
	deformation	ν_8	1030	1008	990
	deformation	ν_9	1280	1262	1229
	twisting	ν_{10}	622	497	435
Non-planar	C–H deformation	ν_{11}	895	902	909
	C–H deformation	ν_{12}	940	940	946

suggest that electron drifts are caused by the halogen atom, leading to alterations in the bending force constants. If the C–H bonds are stiffened on passing from chlorine to iodine, we should expect an increase in the C–H stretching frequencies, but this does not seem to occur.

The overtone and combination bands found in the infra-red and the Raman spectra of vinyl iodide are very satisfactorily explained by using the above fundamentals, as shown in Table I. In the case of vinyl chloride and bromide, it was possible just to resolve some of the Q branches in the bands at about 900 cm.$^{-1}$. The slightly smaller spacing with vinyl iodide has made these not quite resolvable when using the above instruments.

The assignment of fundamentals with the three vinyl halides given above seems sufficiently certain to be used in calculating the thermodynamic properties of these molecules. These calculations will be given in a later paper.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, April 6th*, 1944.]

NOTES.

Pyrolysis of Xanthopinacol and Related Compounds. By ALEXANDER SCHÖNBERG and AHMED MUSTAFA.

IN view of the ready decomposition of xanthopinacol by light (Schönberg and Mustafa, this vol., p. 67) its thermal decomposition is of interest. Bergmann and Schuchardt (*Annalen*, 1931, **487**, 225), decomposing it in toluene or chlorobenzene, isolated only xanthone. We carried out its thermal decomposition under conditions which allowed the preliminary products to be protected from further pyrolysis, and obtained xanthone together with a little xanthen and water. We believe that the thermal decomposition of xanthopinacol proceeds like that of benzopinacol, which yields benzophenone and benzhydrol. Benzhydrol, however, is comparatively stable thermally (Nef, *Annalen*, 1897, **298**, 235), whereas xanthhydrol very readily yields dixanthhydryl ether and water at 150—175° (Kny-Jones and Ward, J., 1930, 535) and the ether is readily decomposed into xanthen and xanthone at higher temperatures.

Corresponding results may be expected from the pyrolysis of pinacols when the decomposition is carried out at temperatures such that the secondary alcohol forms the corresponding ether, which in turn decomposes into the corresponding ketone and methane derivative. The formation of thioxanthen and thioxanthone from thioxanthhydrol at 120—130°, described by Finzi (*Gazzetta*, 1932, **62**, 211) and confirmed by us, may be explained on this basis, as the ether of thioxanthhydrol was not isolated. We obtained also dithiodixanthylen, $S\langle{}^{C_6H_4}_{C_6H_4}\rangle C{:}C\langle{}^{C_6H_4}_{C_6H_4}\rangle S$.

Action of Heat on Xanthhydrol.—While dry carbon dioxide was passing through the apparatus, xanthhydrol (2 g. was heated (bath at 160°) for 2 hours in a tube (A), 25 cm. high, connected by a bent tube to a similar tube (B) containing water, externally cooled. The drops of liquid that collected in the bent tube were shown to be water by the rapid formation of a blue colour with anhydrous copper sulphate. The temperature was then kept at 200° for 20 minutes; a colourless sublimate appeared on the walls of the tube (A) and, on cooling, a pale yellow crystalline residue was left at the bottom. The sublimate, extracted with light petroleum (b. p. 30—50°) and crystallised from methyl alcohol, was shown to be xanthen by m. p. and mixed m. p. The residue crystallised from hot petroleum (b. p. 100—150°) in almost colourless needles and was proved to be xanthone (m. p. and mixed m. p.; blue fluorescence with sulphuric acid).

Action of Heat on Dixanthhydryl Ether.—The ether (5 g.) was heated (bath at 250°) in the apparatus described above; the vapours evolved condensed in the tube (B). The solid in tube (B) was steam-distilled and an ethereal extract of the distillate was dried over anhydrous sodium sulphate and evaporated in a vacuum; colourless crystals of xanthen (m. p. and mixed m. p.) were obtained. The solid in the tube (A), on steam-distillation, gave xanthen and xanthone, which were separated by extraction with hot light petroleum (b. p. 30—50°), in which xanthen is soluble; xanthone was crystallised from hot absolute alcohol and identified as above.

Action of Heat on Xanthopinacol.—(a) Xanthopinacol (5 g.) was heated as in the previous experiments (bath temp. 270°). Xanthen (Found: C, 85·6; H, 5·4. Calc. for $C_{13}H_{10}O$: C, 85·7; H, 5·4%) and xanthone were isolated.

(b) *Detection of water.* The pinacol was placed in a flask carrying a side arm containing two boats filled with anhydrous copper sulphate. The flask was sealed at the neck and evacuated through the side arm (the boats meanwhile being heated to drive out the last trace of moisture), which was then sealed. The apparatus was heated (bath at about 300°) for ½ hour and allowed to cool for 24 hours. The surface of the anhydrous copper sulphate had turned blue, indicating the formation of water. The neck of the flask was filled with crystals of xanthen and xanthone.

Action of Heat on Thioxanthhydrol.—Thioxanthhydrol (2 g.) (Meyer, *Ber.*, 1909, **42**, 1135) was heated at 120—130° (bath temp.) in a pyrex glass tube in a stream of carbon dioxide for 1 hour, a colourless crystalline sublimate being formed. From the product, light petroleum (b. p. 30—50°) extracted thioxanthen (m. p. and mixed m. p.). The residue was extracted with sufficient glacial acetic acid to dissolve the thioxanthone (m. p. and mixed m. p.; colour

reaction with sulphuric acid), leaving a solid which separated from hot xylene in fine colourless crystals of dithiodixanthylen, m. p. above 330°, which gave a blue fluorescence in the solid state (Found : C, 78·9; H, 4·6; S, 16·1. Calc. for $C_{26}H_{16}S_2$: C, 79·5; H, 4·1; S, 16·3%).—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, February 3rd*, 1944.]

Geranylamine. By D. A. SUTTON.

THE published method of preparation of geranylamine hydrochloride has been re-examined with the object of obtaining homogeneous crystals suitable for use in *X*-ray studies of polyisoprenic materials. A preliminary account of the *X*-ray structure of this salt has recently been published from this laboratory (see Bateman and Jeffrey, *Nature*, 1943, **152**, 446). Forster and Cardwell prepared geranylamine from geranyl chloride (J., 1913, **103**, 1338), and converted it, by the action of dry hydrogen chloride in ethereal solution, into the hydrochloride, which darkened at 100° and melted at 120° and has since been considered (Beilstein, supplementary volume 4, p. 398) to be possibly a mixture of $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}NH_3Cl$ (I) and $CH_2{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}NH_3Cl$ (II).

Geranylamine hydrochloride was prepared in the present work in the following way : Commercial geraniol was purified through its calcium chloride compound, and the regenerated alcohol (117 g.) converted into geranyl chloride by the action of phosphorus trichloride (78·4 g.) in petrol solution (see Farmer and Sutton, J., 1943, 116). The middle fraction of the product (74 g.), b. p. 86—110°/12 mm., was treated with sodium azide (44·5 g.) in aqueous alcohol as described by Forster and Cardwell, and the product then reduced by the action of zinc dust (92·5 g.) and acetic acid. The base was liberated by adding an excess of alkali to the acid solution and it was isolated by steam distillation. The fraction of b. p. 90—96°/11 mm. (29 g.) was dissolved in alcohol or acetone (preferably the latter) at room temperature and treated with concentrated hydrochloric acid, drop by drop. Geranylamine hydrochloride was thus obtained in long colourless crystals, m. p. 145—146° (Found : Cl, 19·0; N, 7·6. Calc. for $C_{10}H_{19}N,HCl$: Cl, 18·7; N, 7·4%).

It is clear from Jeffrey's work that the hydrochloride which crystallised in this way had the structure (I), and hence the compound (II), if it is formed at all by the modified procedure, must be the more soluble of the two forms, and remained in solution. It is of interest that geranylamine hydrochloride of m. p. 145—146° affords an unequivocal example of a pure terpenic compound having the end group $CMe_2{:}CH{\cdot}$, which is of importance in connection with the controversy regarding the structure of geraniol, nerol and other terpenes (cf. J. L. Simonsen, " The Terpenes," Vol. I, pp. 34, 43).

The presence of the two forms in Forster and Cardwell's hydrochloride would account for the low m. p. they recorded, although the latter might conceivably be due to addition of hydrogen chloride having occurred at some of the olefinic bonds of the amine.

A waxy solid, m. p. 64—67° [Found : C, 71·65; H, 10·85; N, 7·8. $(C_{10}H_{19}N)_3CO_2$ requires C, 72·0; H, 10·85; N, 8·0%] was formed by exposing the base to the air overnight or more quickly by exposing it to the fumes from solid carbon dioxide. This solid gave very viscous solutions on being warmed with light petroleum, a property which is also characteristic of geranylurea (Forster and Cardwell, *loc. cit.*).—THE BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION, 48, TEWIN ROAD, WELWYN GARDEN CITY, HERTS. [*Received, February 4th*, 1944.]

Constitution of Shellac. The Increased Yield of Aleuritic Acid. By B. S. GIDVANI.

OF the various formulæ which have been proposed for shellac resin (Nagel and Baumann, *Wiss. Veröff. Siemens Konzerns*, 1932, **11**, 99; Nagel and Mertens, *Ber.*, 1937, **70**, 2173; Bhattacharya and Gidvani, *J. Soc. Chem. Ind.*, 1938, **57**, 285; Bhattacharya, *Oil and Col. Trades J.*, 1938, **94**, 1584), the more recent regard it as a condensation product of aleuritic, shellolic and other unidentified hydroxy-acids in equimolecular proportions. This would indicate that, on hydrolysis, about 30% of each acid should be formed. In practice, however, only aleuritic acid is obtained in approximately this yield, the yield of shellolic acid never exceeding 10%.

By the method described below, yields of nearly 43% of aleuritic acid have been secured with some consistency; shellolic acid, on the other hand, was obtained as its dimethyl ester in a yield of only 2·5%. It is unlikely that the whole of the aleuritic acid is isolated, and it is probable that the total amount is in the region of 50%. If the formulæ were correct, such a high yield of aleuritic acid would not have been possible; also shellolic acid should have been obtained in a much greater yield. The formulæ therefore need revision to take into account the greater yield of aleuritic acid which has now been obtained, and also to provide for the new acids isolated by Weinberger and Gardner (*J. Amer. Chem. Soc.*, 1938, **54**, 454).

By conducting a similar process, lead or barium salts being used for separation, the yield of aleuritic acid was reduced to 30% and that of methyl shellolate was increased to 8%. It is suggested that the shellolic acid is not a primary product of hydrolysis, but is formed from unidentified acids or possibly from aleuritic acid itself.

Decolourised and dewaxed shellac (100 g.) was dissolved in 100 c.c. of water containing 20 g. of sodium hydroxide by warming on the water-bath. The hydrolysis was allowed to proceed at room temperature for 10 days. The mixture was then diluted with 100—150 c.c. of 5N-sodium hydroxide, and the liquid filtered through kieselguhr. The sodium salt on the filter was dissolved in the minimum quantity of hot water, and the solution filtered hot. The yield of the sodium salt was 25 g. The filtrate was concentrated on the water-bath, and a further crop of sodium salt (7·5 g.) obtained. Acidification of the sodium salts gave aleuritic acid (nearly 29 g.), identified by mixed m. p. 100—101° and by its methyl ester, m. p. 72—73°.

The filtrate obtained after the separation of sodium aleuritate was treated with a saturated solution of zinc sulphate. The brownish precipitate (48·5 g.) obtained was collected and washed with a little zinc sulphate solution. The washing and the filtrate were mixed and heated, whereby zinc shellolate (5·7 g.), insoluble in hot water, was obtained : methylation of it with methyl alcohol and hydrogen chloride gave methyl shellolate (2·5 g.), m. p. and mixed m. p. 148—150°.

The zinc salts soluble in hot water were acidified with dilute hydrochloric acid; ether then extracted an unidentified amorphous powder (1·8 g.), m. p. 55—70°. The water layer was evaporated to dryness on the water-bath, and the residue extracted with methyl alcohol. The extract was dried over anhydrous sodium sulphate and esterified with hydrogen chloride, giving methyl aleuritate, which, recrystallised from hot water, formed fine feathery needles (2·1 g.), m. p. and mixed m. p. 72—73°.

The brown precipitate (48·5 g.) was extracted with two lots of hot methyl alcohol (55 c.c.). The soluble portion was esterified, and a methyl ester isolated as a brown syrup. Extraction of this with small quantities of boiling water yielded 5·5 g. of methyl aleuritate. The portion insoluble in methyl alcohol was covered with ether and decomposed with dilute hydrochloric acid. The water layer on evaporation gave a resinous film (approx. 1·5 g.). The acids soluble in ether were esterified with methyl alcohol and hydrogen chloride; extraction of the brown syrup with boiling water gave methyl aleuritate (6·8 g.). The total yield of methyl aleuritate was 2·1 + 5·5 + 6·8 g., equivalent to 13·8 g. of aleuritic acid.—LAC RESEARCH LABORATORY, 79 GRASSMARKET, EDINBURGH, 1. [*Received, March 6th*, 1944.]

An Easy Method for the Preparation of Dianthraquinone. The Action of Pyridine on Dianthranol and Dianthrone.

By Alexander Schönberg and Abdel Fattah Aly Ismail.

Dianthranol is rapidly oxidised (in excellent yield) at room temperature to dianthraquinone by *p*-benzoquinone, with formation of quinhydrone.

Dianthranol or dianthrone, when treated with pyridine, yields a yellow crystalline *substance*. It remains unchanged in a closed vessel for 3 months at the ordinary temperature, but loses pyridine when heated. When treated with alcoholic hydrogen chloride, it yields dianthrone.

Preparation of Dianthranol (Dianthrol) from Dianthrone (compare Meyer, *Monatsh.*, 1909, **30**, 174).—Dianthrone (10 g.) was refluxed for 1 hour with alcohol (140 c.c.) containing potassium hydroxide (3·92 g.). The solution was then cooled and acidified slowly with ice-cold concentrated hydrochloric acid. The crystalline product was dried on a porous plate and recrystallised from alcohol, giving dianthranol in almost quantitative yield.

Preparation of Dianthraquinone.—Dianthranol (10 g.) and *p*-benzoquinone (11·2 g.), dissolved or suspended in acetone (200 c.c.), were kept at room temperature for ½ hour with occasional shaking. The precipitate was collected and washed with acetone until its colour was citron-yellow. The dianthraquinone (yield, almost quantitative), after recrystallisation from xylene, had m. p. and mixed m. p. above 300°. Its tetrachloroethane solution showed the colour phenomena described by Meyer (*loc. cit.*) (Found : C, 87·3; H, 4·1. Calc. for $C_{28}H_{16}O_2$: C, 87·5; H, 4·1%).

The acetone filtrate was evaporated to dryness; the residue, benzene-distilled until the distillate was almost colourless, in order to remove the excess of *p*-benzoquinone, and then washed with benzene, was quinhydrone, m. p. and mixed m. p. 170°.

Preparation of the Pyridine Compound.—(a) *From dianthrone.* Dianthrone (10 g.) was refluxed with pyridine (75 c.c.) for 2 hours. The deep yellow, crystalline product which separated on slow cooling was washed with dry ether (yield, 10 g.), recrystallised several times from pyridine, and washed with dry ether. The yellow crystalline *compound* obtained (Found : C, 83·0; H, 5·1; N, 5·0. $C_{28}H_{28}O_2N_2$ requires C, 83·8; H, 5·2; N, 5·2%) melted at 190° with evolution of gas; when this ceased, the residue solidified on cooling and then melted at about 229° (the m. p. of dianthranol is about 230°).

(b) *From dianthranol.* Dianthranol (1 g.) was refluxed with pyridine (15 c.c.) for ½ hour; on cooling, yellow crystals separated, identical with the product, m. p. 190°, obtained above.

The pyridine compound (1 g.) was refluxed for 3 hours with alcohol (50 c.c.) saturated with hydrogen chloride. After 12 hours, crystals of dianthrone separated, m. p. and mixed m. p. 250° after recrystallisation from petroleum (b. p. 100—150°).—Fouad I University, Cairo, Egypt. [*Received, February 3rd*, 1944.]

The Constitution of Belmacamgenin and Belmacamdin.

By S. Wang (Wang Hsin) and M. Hu (Hu Mei).

From *Sheh Kan* (*Belmacamda Sinensis*, Lam. Iridaceæ), the chief remedy for tonsillitis in the Chinese materia medica, a neutral crystalline substance, m. p. 63—65°, was isolated by Wang and Ho (Thesis, University of Chekiang, 1941). The present authors have now isolated another compound, a colourless crystalline glucoside, which they have named belmacamdin.

Belmacamdin is hydrolysed by 10% alcoholic hydrogen chloride, yielding glucose and belmacamgenin. Belmacamgenin forms an acetyl derivative, a dimethyl ether having the same melting point (162°) as trimethylirigenin (Baker, J., 1928, 1022), and molecular-weight determinations (Rast) and estimation of methoxyl indicate that it is a pentahydroxymonomethoxy*iso*flavone.

Methylation of belmacamdin with methyl sulphate and alkali, followed by hydrolysis with alcoholic hydrogen chloride, yields a compound, m. p. 165°, identical with 7 : 3′-dimethylirigenin (Baker, *loc. cit.*).

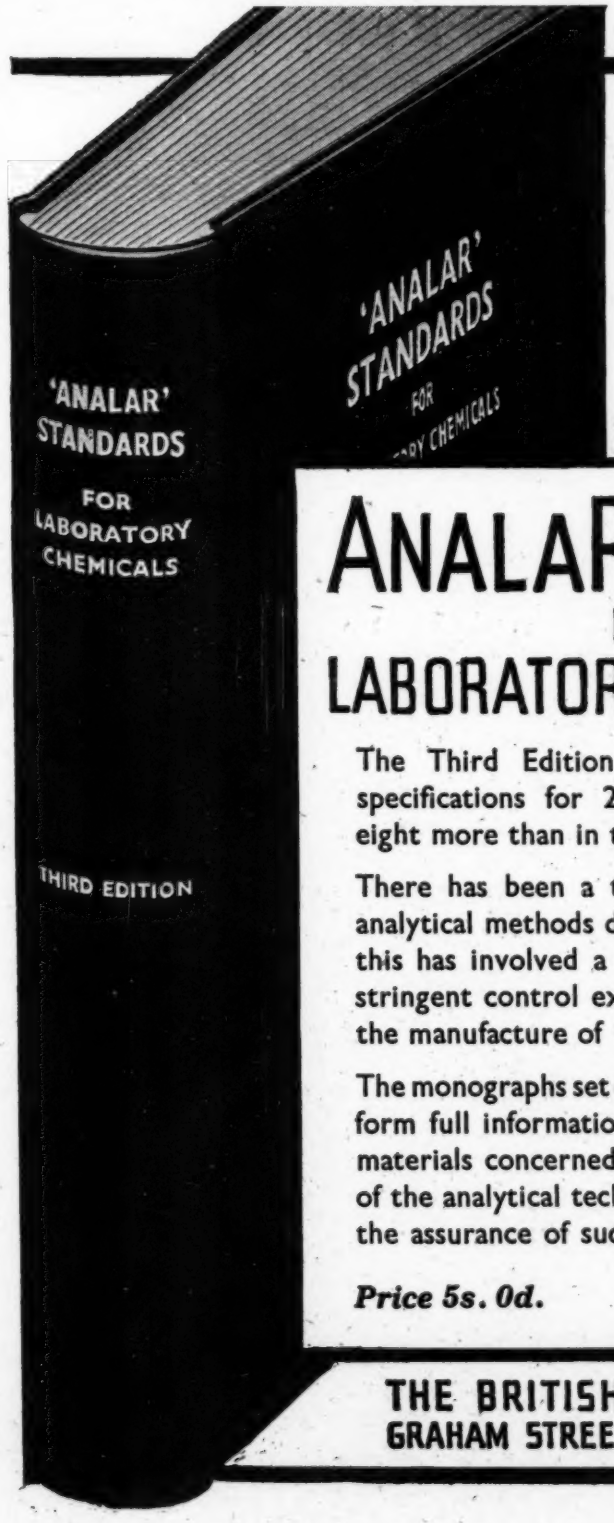
Belmacamdin.—Powdered root of *Belmacanda* (300 g.) was refluxed 3—4 times for 2 hours with alcohol (500 c.c.). The extracts were filtered while hot, united, and concentrated to small volume. The glucoside slowly separated as a thick crystalline paste, which was digested three times with a small amount of cold alcohol, once with ether, and finally with cold water to remove glucose. Belmacamdin thus purified was a white crystalline powder, m. p. above 300°, and could be recrystallised from a large amount of alcohol (yield 6 g.; 2%). It gave a violet coloration with alcoholic ferric chloride.

Belmacamgenin.—Belmacamdin (6 g.) was refluxed with 10% alcoholic hydrogen chloride (200 c.c.) for 6 hours, and the brown solution then concentrated to small volume and diluted with water. The precipitate was collected and recrystallised twice from dilute alcohol. Belmacamgenin formed pale yellow needles (3 g.), m. p. 227°, and gave with ferric chloride a dark green coloration which became greenish-brown on boiling [Found : OMe, 8·2; *M* (Rast), 337. Calc. : 1OMe, 9·3%; *M*, 334].

Methylation. Belmacamgenin (0·2 g.) was dissolved in N-potassium hydroxide, and methyl sulphate (5 c.c.) and 33% potassium hydroxide solution (8 c.c.) added simultaneously with shaking and cooling. The product, collected after 12 hours and recrystallised with alcohol, had m. p. 162°.

Acetylation. Belmacamgenin (0·2 g.) was refluxed with acetic anhydride at 160° for 6 hours. After dilution with water the crystalline product slowly separated, m. p. 184—185° after recrystallisation from alcohol.

Methylation of Belmacamdin.—This was carried out as in the case of belmacamgenin. Belmacamdin (0·5 g.) gave a colourless oil, which, after being washed with ether, was refluxed with alcoholic hydrogen chloride for 4 hours. The alcoholic solution was concentrated and diluted with water; the precipitate obtained, after recrystallisation from alcohol, had m. p. 166°.—National Academy of Peiping, Kunming, China. [*Received, January 29th*, 1944.]



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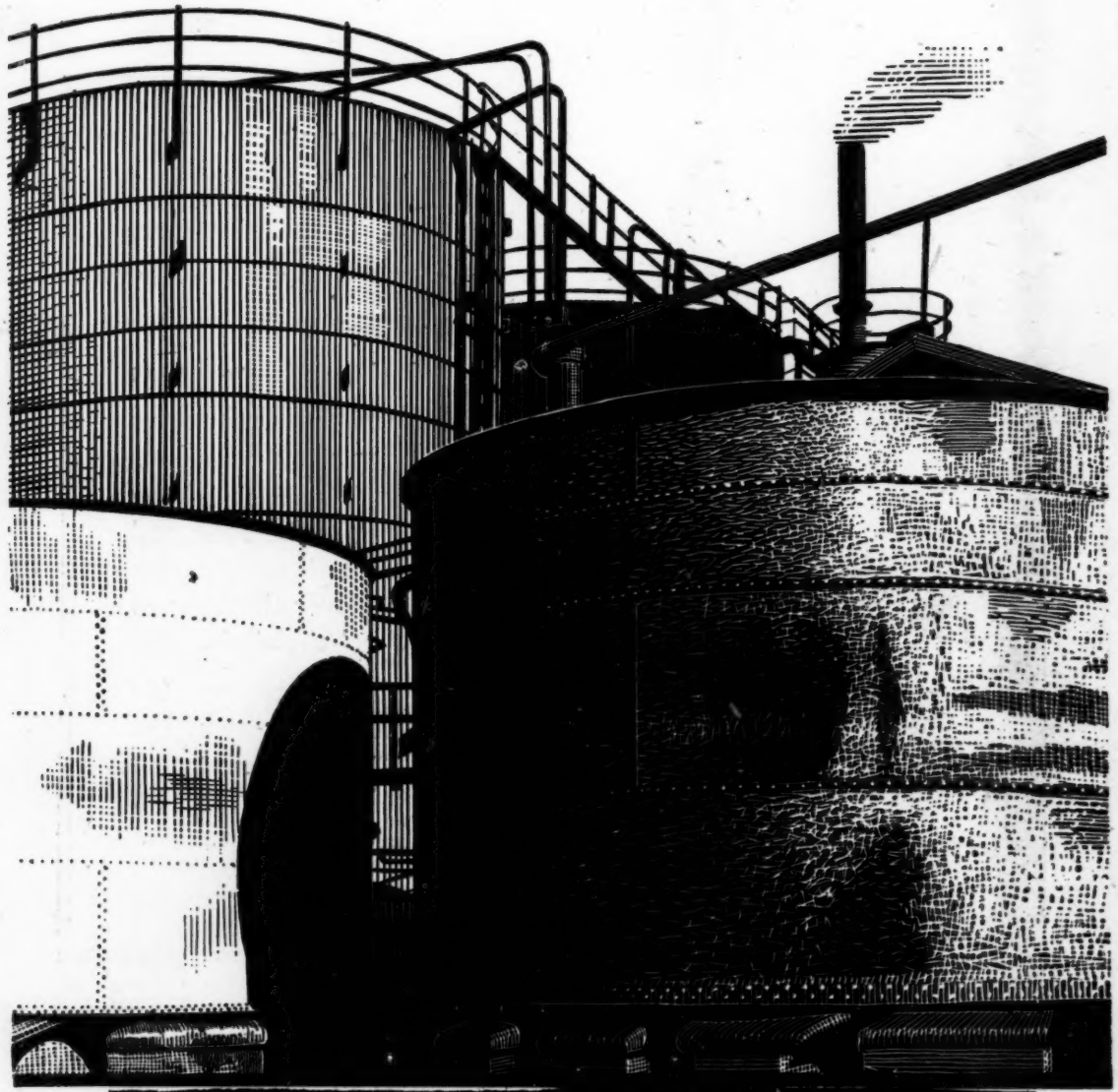

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